ON THE MECHANISM OF THE EFFECT OF PHENAMINE ON THE PITUITARY – ADRENAL SYSTEM

(UDC 615.785-092.259:[612.432+612.45])

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(Presented by Member of the Academy of Medical Sciences USSR, N. I. Grashchenkov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 2, pp. 64-67, February, 1966
Original article submitted May 14, 1964

It is known that phenamine stimulates the function of the pituitary–adrenal system [9]; however, the mechanism of this influence has not been studied.

In this work, we undertook to determine the degree to which the stimulating effect of phenamine upon the pituitary–adrenal cortex system is related to its central adrenomimetic effect, and to what degree it depends upon the influence of phenamine on the peripheral adrenoreactive structures.

EXPERIMENTAL PROCEDURE

The experiments were conducted on 67 male guinea pigs, weighing 450-730 g. Phenamine, in the form of a 1% solution in distilled water, was injected subcutaneously in amounts of 10 mg per kg of weight. The control animals received subcutaneous injections of the corresponding amount of distilled water.

Under brief ether narcosis, the guinea pigs were scalped, after which a small trepanning opening was made on the right side of the skull with a dental drill. The brain was cut with a spatula, and narcosis was immediately stopped. The section was both of the pretrigeminal character (the brain was cut across behind or along the posterior corpora quadrigemina and along the anterior third of the pons variolii), and of the type of cerveau isolé according to Bremer [4] (the plane of the section passed between the corpora quadrigemina and in front of the pons). Such sections made it possible to cut off all the peripheral impulsation, except for the nerve pulses running along the first and second pairs of craniocerebral nerves. To maintain normal body temperature of the animals after sectioning of the brain, they were warmed with heaters and an electric lamp.

The EEG and ECG were recorded on the ink-writing encephalograph produced by "Kaiser" Company. The electrical potentials were drawn off from the sensomotor and parietal regions of the cerebral cortex with the aid of implanted needle electrodes, with an electrode gap of 3 mm. The ECG was taken in the second standard takeoff.

Among intact animals, the blood was taken from the heart an h after the injection of phenamine or the corresponding amount of distilled water. In experiments with brain sections, the first blood sample was taken from the heart an h after cutting, after which phenamine or distilled water was immediately injected subcutaneously. A second blood sample was taken an h after the injection (2 h after cutting).

In preliminary experiments to determine the functional state of the hypothalamic–pituitary–adrenal system against a background of section of the brain, the guinea pigs were rapidly injected with 0.3 ml of cold physiological saline with a 5% glucose solution into the right lateral lobe of the brain through an implanted cannula, an h after the operation. The level of corticosteroids in the peripheral blood of the animals, which was determined according to Yudaev and Pankov [3], was used as the index of a change in the activity of the pituitary–adrenal system.

To monitor the conduction of the vessels among animals with sections of the brain stem, methylene blue was injected into the carotid artery after the experiments. The site of cutting of the brain and position of the cannula

TABLE 1. Corticosteroid Content (in μg %) in the Blood of Control Animals with Sections of the Brain Stem

Series of experiments	Blood sample	17-hydroxy-corticosteroids M ± m	P	No. of animals
Control	1 h after sectioning	64.26 ± 8.74	>0.1	8
	2 h after sectioning	70.09 ± 8.49		
Injection of cold physiological saline into lateral ventricle of brain	1 h after sectioning	61.95 ± 3.83	<0.001	24
	2 h after sectioning	119.86 ± 7.52		

TABLE 2. Content of Corticosteroids (in μg %) in the Blood of Intact Animals and Animals with Section of the Brain Stem as a Result of the Injection of Phenamine

Animals	Blood sample	17-Hydroxy-corticosteroids M ± m	P	No. of animals
Intact	Initial	42.45 ± 3.52	<0.001	14
	1 h after injection of phenamine	138.69 ± 9.0		
With section of brain stem	Initial	63.22 ± 4.72	>0.1	21
	1 h after injection of phenamine	74.74 ± 8.01		

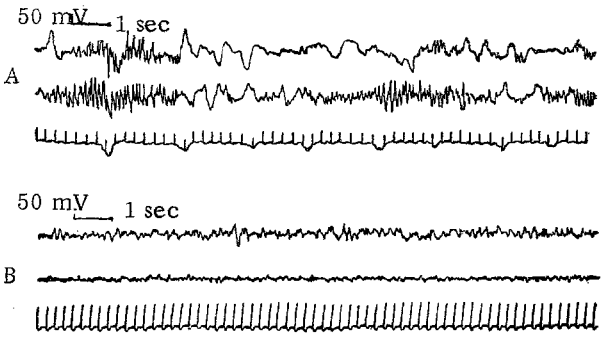
in the lateral ventricle in all cases were checked immediately after killing of the animals or after fixation of the brain in formalin.

EXPERIMENTAL RESULTS

In the control animals, after cutting of the brain stem, the level of 17-hydroxycorticosteroids in the peripheral blood plasma was unchanged during the experiment. The injection of cold physiological saline into the lateral ventricle of the brain induced a substantial increase in the corticosteroid content in the blood, which was evidence of the functional activity of the hypothalamic–pituitary–adrenal system against a background of sectioning of the brain (Table 1).

An h after subcutaneous injection of phenamine (10 mg/kg) into animals with an intact brain, a sharply increased content of 17-hydroxycorticosteroids was noted in the peripheral blood plasma. At the same time, against a background of section of the brain stem, the level of corticosteroids was unchanged in comparison with the initial level an h after the injection of phenamine (Table 2). The absence of a response to phenamine was observed both in the case of pretrigeminal sections a id in the case of cerveau isolé ($P > 0.1$). This gave a basis for considering the results of the experiments obtained on these two groups as unambiguous.

In the case of sections of the brain stem, simultaneously with our investigation of the corticosteroid content in the blood, we studied the bioelectric activity of the brains of the animals. After the injection of phenamine, an activation of the EEG was noted in the sensomotor and parietal regions of the cerebral cortex, the appearance of a low amplitude frequent rhythm. Such a change in the bioelectric activity of the brain was especially distinct in the case of pretrigeminal sections (see figure). The activating effect of phenamine was also retained in the case of cerveau isolé, but it was less pronounced than in animals with pretrigeminal section of the stem and was manifested in a decrease in the amplitude and a certain speed up in the recorded rhythm.



EEG and ECG before (A) and 32 min after (B) injection of phenamine into guinea pigs with pretrigeminal section of the brain stem. From top to bottom: EEG of sensomotor and parietal region of cerebral cortex; ECG.

Thus, the absence of an effect of phenamine upon the hypothalamic–pituitary–adrenal system in the case of pretrigeminal sections and cerveau isolé cannot be explained by a disruption of the blood circulation in regions of the brain lying above the level of the section, since in this case a change in the bioelectric activity of the cerebral cortex is observed and, moreover, the vessels of the brain above the level of the section are well colored after intraarterial injection of dye.

Consequently, the regions situated above the level of the section probably do not take part in the mechanism of stimulation of the function of the pituitary–adrenal system, observed under the action of phenamine upon animals with intact brains. It might be thought that the change in the functional state of the adrenal cortex noted against a background of the action of phenamine is due to excitation of the peripheral adrenal reactive structures. The data that we obtained earlier [1,2] on the absence of any influence of pyridrol, a preparation that excites the central adrenoreactive structures and has practically peripheral adrenomimetic effect upon the corticosteroid level in the blood of the guinea pigs, may serve as a confirmation of this hypothesis. At the same time, naphthizine, an adrenomimetic substance with peripheral action, induces a sharp increase in the content of 17-hydroxycorticosteroids in the blood upon subcutaneous injection.

In recent years, a number of studies of Egdahl [5-8] have appeared in which the author proposed on the basis of his experiments with removal of the brain (at various levels) that the hindbrain may be the source of the manufacture of a humoral factor of unknown character, which may exert a stimulating effect upon the pituitary–adrenal system. However, this opinion will need further evidence, all the more in that experiments with complete removal of the brain have given some authors [10] a basis for not confirming this hypothesis.

Naturally, the possibility of the participation of the corresponding chemoreactive structures of the caudal portion of the hindbrain in the mechanism of the stimulating effect of phenamine upon the pituitary–adrenal system cannot be entirely eliminated on the basis of our experiments. This question will require further study.

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