THE MECHANISM OF DIPHACYL'S (SPASMOLYTIN, TRASENTINE) EFFECT ON THE ADRENAL CORTICAL FUNCTION

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According to S. V. Anichkov [1], Diphacyl belongs to the group of substances which act primarily on the central cholinergic synapses.

Experimental investigations carried out in Prof. S. V. Anichkov's laboratory [6, 7, 8] have shown that Diphacyl reduces the ascorbic acid content of rats' adrenal glands and causes eosinopenia in the peripheral blood of animals (rats, rabbits). These are indices of increased adrenal cortical function [3, 4, 12].

We made a direct assay of the 17-hydroxycorticosterones in the peripheral blood of dogs [2]. We determined the 17-hydroxycorticosterones by the Silber and Porter method, as modified by N. A. Yudaev and Yu. A. Pankov [10], and obtained statistically significant data showing that Diphacyl [diphenylacetic acid diethylaminoethyl ester] almost triples the 17-hydroxycorticosterone content of the blood.

We then proceeded to investigate the action mechanism of Diphacyl responsible for the increase in the hormone content of the blood.

In experiments on decerebrate cats [6, 7], we observed that Diphacyl only increases adrenal cortical activity when the hypophysis and hypothalamus are intact. This suggested that the hypophysis plays a role in the intensification of the adrenal cortical function.

We decided to analyze the mechanism of Diphacyl's action and determine to what extent Diphacyl's intensifyingeffect on the adrenal cortical function is connected with its central cholinolytic effects.

EXPERIMENTAL METHODS AND RESULTS

This article reports the results of experiments performed on 17 male white rats weighing 150-200 g each.

In one experimental series, we performed hypophysectomy on intact rats by E. M. Silaeva's method (see [9]). The experiments on the rats were usually made 24-35 hours after the hypophysectomy. One group of hypophysectomized rats served as the control; the rats of this group were intraperitoneally injected with distilled water and then sacrificed by decapitation 50-90 min later. The adrenal glands were removed through a dorsal incision and decapsulated, after which their ascorbic acid content was determined by means of Tilman's stain.

Each of the other group of hypophysectomized animals were given Diphacyl, intraperitoneally injected in a dose of 20-50 mg/kg. In this case too, the ascorbic acid content of the adrenal glands was determined 50-90 min after the administration of Diphacyl.

Effect of Diphacyl on Ascorbic Acid Level in Adrenal Glands of Hypophysectomized Rats

Experiment date (1959)	Diphacyl dose (in mg/kg)	Ascorbic acid content (in mg %)		Number of rats in group
		after Diphacyl	control	
5/IX	50	549	565	2
9/IX	50	558	524	1
14/IX	50	579	573	1
16/IX	50	586	514	1
18/IX	30	550	518	2
24/IX	30	567	516	2
26/IX	30	580	544	1
28/IX	30	501	514	1
2/X	30	540	500	2
3/X	20	527	523	2
8/X	30	420	466	2
Average		541	523	

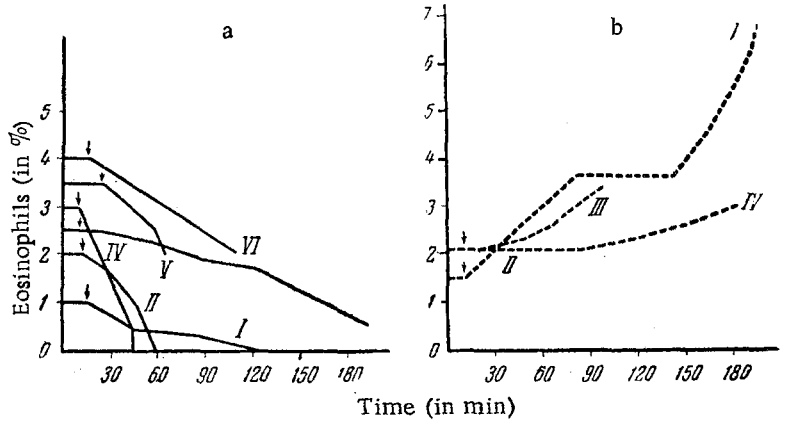


Fig. 1. Effect of Diphacyl on eosinophil content in peripheral blood of intact (a) and adrenalectomized (b) rats. Arrow ( ) shows intraperitoneal injection of Diphacyl (50 mg/kg).

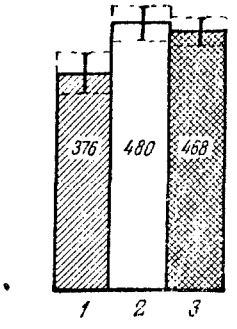
The experimental results showed that Diphacyl, administered after hypophysectomy, caused no decrease in the ascorbic acid content of the rats' adrenal glands, but caused, on the contrary, some increase. This increase in ascorbic acid content was not, however, statistically significant. The results of this experimental series are shown in the table.

The results of these experiments led us to conclude that the hypophysis is of essential importance to Diphacyl's activating effect on the adrenal cortical function.

To further analyze Diphacyl's action mechanism, we performed a series of experiments to determine Diphacyl's effect on level of eosinophils after adrenalectomy.

Experiments on four rats showed that Diphacyl did not cause marked eosinopenia in the adrenalectomized animals; eosinophilia was even observed in a few experiments (Fig. 1).

In order to ascertain the extent to which the central effect of Diphacyl promotes adrenal cortical activation, we investigated Diphacyl's effect and that of its quaternary analog, Diphacyl iodoethylate on the adrenal cortex of intact rats.



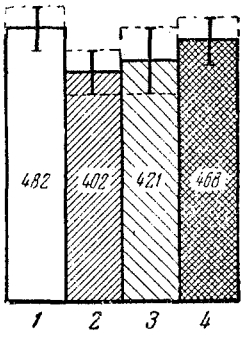


Fig. 2. Fig. 3.

Fig. 2. Effect of Diphacyl and Diphacyl iodoethylate on ascorbic acid level in rats' adrenal glands. Each column represents the average ascorbic acid content (in mg %) in the adrenal glands of 45 rats. Top – absolute limits. 1) 50-90 min after intraperitoneal injection of 20-50 mg/kg Diphacyl; 2) control; 3) 50-90 min after intraperitoneal injection of 30-50 mg/kg Diphacyl iodoethylate.

Fig. 3. Ascorbic acid content in adrenal glands of rats following administration of Diphacyl and proserine. Each column represents the average ascorbic acid content (in mg %) in the adrenal glands of 32 rats. Top – absolute limits. 1) control; 2) 50-90 min after intraperitoneal injection of Diphacyl (30 mg/kg); 3) 50-90 min after intraperitoneal injection of proserine (neostigmine] (0.1 mg/kg); 4) 50-90 min after administration of Diphacyl (30 mg/kg) and proserine (0.1 mg/kg) in combination.

According to the literature data [5, 11], the peripheral effect of Diphacyl's quaternary analogs on the biochemical systems of the tissues is stronger than their central effect.

Our experiments showed that Diphacyl iodoethylate caused no statistically significant increase in the cortical activity of the adrenal glands (Fig. 2).

Therefore, Diphacyl's central effect is of prime importance to its effect on the hypophysial-adrenal system. Diphacyl probably facilitates the secretion of ACTH by hypophysis by activating certain hypophysial-hypothalamic centers.

The works of Bovet and Longe [11] and N. A. Kharauzov [9] have shown that the effects of cholinomimetic and cholinolytic agents can be antagonistic in the region of the central cholinergic synapses.

To determine whether Diphacyl's activating effect on the hypophysial-adrenal system is associated with its central cholinolytic effect, we performed experiments on rats to which Diphacyl and anticholinesterase substances were administered. In previous experiments [8], we had observed that Diphacyl's effect on the hypophysialadrenal system is removed by the anticholinesterase substance physostigmine. In the subject series of experiments on rats, we established that another anticholinesterase substance, proserine, distinctly nullifies Diphacyl's effect on adrenal cortical activity. The results of this series of experiments are given in Fig. 3.

It is clear from Fig. 3 that Diphacyl's activating effect on the hypophysialadrenal system is weakened in the presence of cholinomimetic substances, which are antagonistic to cholinolytics. Therefore, the activation of the adrenal glands effected by Diphacyl is associated with its effect in the region of the central cholinergic synapses.

SUMMARY

The author studied the mechanism of Diphacyl action upon the cortical activity of adrenal glands in white male rats. Diphacyl enhances the activity of the adrenal cortex (reduces the ascorbic acid content therein, provokes eosinopenia in the peripheral blood system) only in intact animals, and not in hypophysectomized rats. Experiments with the administration of Diphacyl is connected with its central action. Anticholinesterase substances reduce the action of Diphacyl on the hypophysis-adrenal system. Consequently the stimulating effect of Diphacyl upon the adrenal function is associated with the action of this preparation in the area of the central cholinergic synapses. At the expense of this effect, Diphacyl possibly facilitates the secretion of ACTH of the hypophysis, stimulating the discharge of 17-hydroxycorticosterones into the blood.

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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.
