ROLE OF THE HYPOPHYSIS IN THE RESISTANCE OF RATS TO DIPHTHERIA TOXIN

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Of the investigations into the role of the hypophysis in the resistance of animals to various pathogenic factors, comparatively few are devoted to resistance to diphtheria toxin [4, 7, 15]. Frick and Lamp [7] found that hypophysectomized guinea pigs have a lower survival rate than do normal animals.

Skuratova (1956) has shown that introduction of ACTH at the time of immunization with diphtheria toxoid raises the resistance of guinea pigs to subsequent injection of diphtheria toxin, as compared with control animals. A similar effect is found when ACTH is injected 3 months before the injection of diphtheria toxin, with subsequent repeated doses of ACTH at various times before injection of toxin, and simultaneously with its injection.

We thought it would be instructive to examine the resistance of albino rats to diphtheria toxin; these animals are reported [8] to be 5000-10,000 times more resistant than guinea pigs.

The object of the present research was to investigate the effects of hypophysectomy and of administration of ACTH to hypophysectomized rats on their resistance to diphtheria toxin.

EXPERIMENTAL METHODS

The animal material consisted of 64 female albino rats, weighing from 140 to 190 g; of these, 48 were hypophysectomized, and 16 were controls. The control animals were subjected to a dummy operation, involving the same operational manipulations, but without removing the hypophysis. Hypophysectomy was performed by a paratracheal approach, described by Sllaeva [3]. The daily dose of ACTH (6 mg per 100 g body weight) was dissolved in 1% sodium chloride solution, and injection subcutaneously into the left thigh, in 3 doses, with a 12 hour night interval. The animals were given ACTH during the whole period of intoxication (8-10 days). The first injection of ACTH was given 1 hour before injection of diphtheria toxin. The first series of experiments was performed on 16 controls and 16 hypophysectomized rats. Ten days after the operation both groups of animals were given diphtheria toxin (guinea pig MLD = 0.0026 ml). In the second series of experiments two groups of 16 hypophysectomized mice were taken, 10 days after the operation. The rats of the first group, which served as controls, did not receive ACTH, while those of the second group were given ACTH, according to the above schedule. All rats were then given diphtheria toxin. Only animals in which the total absence of hypophyseal tissue had been confirmed were taken for these experiments. Completeness of hypophysectomy was checked by histological examination of the ablated gland, by visual examination of the hypophyseal cavity, using a binocular lens, by comparison of the absolute eosinophil count of the peripheral blood before and after hypophysectomy, and by the adrenalin test (a modification of Thorn's test [14]). LD_{50} was determined according to Reed and Muench [11].

EXPERIMENTAL RESULTS

The results, presented in the Table, show that LD_{50} for diphtheria toxin is smaller for hypophysectomized than for intact rats (0.247 and 0.418, respectively). It is evident from a comparison of the number of rats dying and surviving that mortality is higher in the hypophysectomized group. The length of the survival time in the two groups also shows that hypophysectomy leads to a fall in resistance to diphtheria toxin.

A similar comparison of the data for hypophysectomized rats receiving and not receiving ACTH indicates that adrenocorticotrophic hormone raises the resistance of hypophysectomized rats to diphtheria toxin.

Hypophysectomy is followed by dysfunction of numerous endocrine glands, and by disorganization of numerous processes concerned with hypophyseal function. In this connection, the regulatory function of the central nervous system is profoundly disturbed [5]. Of the large number of factors leading to lowering of resistance of hypophysectomized rats, we attach special importance to those connected with hypophyseal-adrenal relations, since it is these which, according to numerous authors, are responsible for determining the resistance of the organism to the action of harmful factors.

Resistance of Hypophysectomized and Control Rats to Diphtheria Toxin

Indicators of resistance / Animals	LD_{50}	Number of rats dying and surviving* — dose of toxin, in ml per 100 g body weight						Mean survival time (days)
		0.615	0.473	0.364	0.28	0.21	0.16	
Intact	0.418	4/0	3/1	1/3	0/4	0/4		7.8
Hypophysectomized	0.247	4/0	1/0	7/1	4/4	1/3	1/3	6.1
Hypophysectomized, given ACTH	0.303			4/0	3/1	2/2	0/4	7.4

* Numerator: number of rats dying; denominator: number surviving.

The protective effect of the adrenals in diphtheritic intoxication was shown by Bogomolets [1], Molchanov [2], and, later, by Lewis and Page [9], Yurkov [6], and others.

It is noteworthy that corticoadrenal extracts and individual corticosteroids are effective in raising the resistance of adrenalectomized rats only, to diphtheria toxin, but have no significant effect in intact animals [8, 9].

Of the individual corticosteroids, only glucocorticoids (compound A acetate) raise the resistance of adrenalectomized rats to diphtheria toxin; desoxycorticosterone acetate was without effect [9].

According to a number of authors [12, 14], the adrenocorticotrophic hormone of the anterior hypophysis is active chiefly in stimulating secretion of glucocorticoids.

If we accept Selye's view [13] that the hormone reaction is triggered by ACTH secretion, it would follow that the protective action of the adrenal cortex could not be fully developed in the absence of the hypophysis. This supposition is supported by the finding that administration of ACTH to hypophysectomized rats raises their resistance to diphtheria toxin. Skuratova's findings [4] also supports this view.

Our experimental findings support the view that the hypophysis plays a significant part in the determination of the natural resistance of rats to diphtheria toxin. It is probable that this protective effect is mediated through its adrenocorticotrophic function. Other pituitary hormones may of course, also exert a protective action, since ACTH administration raises the survival rate of hypophysectomized rats by only 10%, as compared with hypophysectomized rats not receiving ACTH, whereas hypophysectomy lowers their resistance by over 40%.

SUMMARY

It was established that hypophysectomy causes decreased resistance of rats to diphtheria toxin. LD_{50} of diphtheria toxin is less for hypophysectomized rats than for intact ones. It equals correspondingly 0.247 and 0.418. Introduction of ACTH to hypophysectomized animals increased their resistence to diphtheria toxin (LD_{50} equaled 0.303).

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* In Russian.