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Effect of Adrenalin on Resistance of Adrenalectomized Rats to Certain Toxic Agents. (22274)

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Prior to 1917, the secretion of the adrenal medulla was believed to be the entity which rendered the adrenal glands indispensable for maintenance of life(1). Following the demonstration that epinephrine-free cortical extracts maintained normal blood sugar levels in adrenalectomized rats(2), the role of the medullary hormone has generally been regarded as of minor importance, if any. In searching for a rapid method of assay for DOC-like activity of steroids, it was observed that adrenalin rather than cortical steroids conferred resistance to administration of certain toxic agents in adrenalectomized rats. The sequence of events which led to this finding is here described. On the premise that adrenalectomized animals exhibit decreased tolerance to administered potassium(3), the proposed method of assay was to determine the amounts of cortical steroids which would provide increased resistance to the injection of potassium chloride.

Methods. Intact and adrenalectomized male albino Sprague-Dawley rats, one-half of each group having been treated with desoxycorticosterone acetate, 1 mg rat/day up to 7 days, were injected subcutaneously with 0.5 cc of 10% potassium chloride solution every 10 minutes until death, and the number of injections given up to the time of death was recorded. It was noted that adrenalectomized animals succumbed after only one-half as many injections as those given intact animals, and that even intensive pretreatment with DCA did not diminish the susceptibility of adrenalectomized rats to injected potassium chloride.

Results. Since, in some of the adrenalectomized rats, convulsions suggestive of hypoglycemic shock were noted after only one or 2 injections of KCl, glucose determinations were made on blood collected from the heart at the instant of respiratory failure. These values are shown in Table I.

TABLE I. Blood Sugar of Intact and Adrenalectomized Rats Injected with KCl.

Blood sugar (mg %)*	Untreated	KCl-treated
Intact	135	275
Adrenalectomized	85	45

* Pool of 4 animals.

The blood sugar values confirmed the impression that adrenalectomized rats were indeed in a hypoglycemic state, and also showed that intact animals exhibited an increase in

TABLE II. Effects of Adrenalectomy, Adrenal Demedullation, and Administration of DCA, Cortisone, and Adrenalin on Sensitivity to KCl.

No. of inj.	4	5	6	7	8	9	10	11	12	13	14	15	16	Blood sugar (mg %) Initial	Terminal
No. of deaths:															
Intact			2	3	4		1	2						130	270
Adx.	5	3	1	2	1									115	40
" + DCA	4	3		3	2									155	80
" + cortisone	1	1	3	3	2	1	1							135	75
Demedullated	1	2	2	3	3			1						—	125
Adx. + adrenalin				2	4	2			1	2			1	110	240

blood sugar. It was thereupon decided to investigate whether the hypoglycemic response of the adrenalectomized rats could be modified by the administration of glucocorticoids, and if so, whether their sensitivity to KCl could thereby be reduced. In addition, since the ablation of adrenals deprives the animal of another hyperglycemic factor, the medullary secretion, the study was extended to include the effect of adrenalin administration. One group of adrenalectomized rats was treated for 7 days with 1 mg cortisone acetate injected subcutaneously/rat/day. On the 8th day they were injected with KCl as in the foregoing test. Another group of adrenalectomized rats was injected with a solution of KCl, each 0.5 cc containing 10 γ of adrenalin chloride. A third group consisted of rats whose adrenals had been enucleated 1 month previous to the test. The remaining groups included DCA-treated adrenalectomized rats, and untreated intact and adrenalectomized controls. Blood sugars were collected terminally.

The results (Table II) confirmed the previous findings that untreated adrenalectomized rats tolerated less KCl than intact animals and that DCA-treated adrenalectomized rats showed the same sensitivity to KCl as untreated adrenalectomized animals. They also demonstrated that cortisone-treated adrenalectomized rats and demedullated rats were only slightly less sensitive to KCl than adrenalectomized animals and that adrenalin-treated adrenalectomized rats tolerated KCl as well as or possibly better than did intact rats. Hyperglycemia was present in the intact and in the adrenalin-treated rats; the cortisone- and DCA-treated groups and the demedullated rats showed a lower blood sugar level than the intact rats. The untreated adrenalectomized animals exhibited hypoglycemia.

In view of the protection given by adrenalin, this treatment was tested against 2 other arbitrarily selected toxic agents, formaldehyde and sodium arsenite. The former was injected subcutaneously in doses of 0.1 cc of a 10% solution; the latter in 0.5 cc doses of a 1% solution. The results (Tables III and IV) show that adrenalin increased the resistance of adrenalectomized rats to both reagents. In the case of formaldehyde, however, the adrenalin-treated adrenalectomized rats were still more sensitive than the intact animals, while with sodium arsenite, the adrenalin-treated adrenalectomized rats were, if anything, somewhat more resistant than the intact rats.

TABLE III. Effect of Adrenalin in Formaldehyde Poisoning.

No. of inj.	5	6	7	8	9	10
No. of deaths:						
Intact			1			*
Adrenalectomized	3		1		1	
Adx. + adrenalin		1	1	1	1	1

* Of 5 intact animals, all but one were still alive after 10 injections, although they were in a state of collapse.

TABLE IV. Effect of Adrenalin in Sodium Arsenite Poisoning.

No. of inj.	3	4	5	6	7
No. of deaths:					
Intact	1	6			1
Adrenalectomized	4	3			1
Adx. + adrenalin			6	2	

Although the increased resistance in adrenalin-treated animals was always accompanied by a rise in blood sugar, the hyperglycemic

TABLE V. Comparative Effects of Adrenalin and L-arterenol.

No. of inj.	3	4	5	6	7	8	9	10	11	12	Blood sugar (terminal) mg %
No. of deaths:											
Adx. + KCl	1	6	3	2	1						105
" + adrenalin		1	2	2	2	1	1	2	1	1	185
" + L-arterenol			4	3	3		2	1			135

state appeared to be merely a measure of adrenalin activity and not the mechanism responsible for survival. The blood sugar level in the adrenalectomized rats, even terminally, was never so low as to permit an assumption that hypoglycemia was the immediate cause of death. It seemed likely that the primary effect of adrenalin was to resist circulatory collapse. Since l-arterenol (nor-epinephrine) is known to maintain vasomotion while only slightly raising the blood sugar level, the effects produced by this agent should reveal the significance of the hyperglycemia, if any. L-arterenol was therefore administered in the same manner as was adrenalin. The results (Table V) showed that adrenalin and l-arterenol had comparable effects.

It appeared, then, that the supportive effect of the medullary hormone was primarily in maintaining vascular tone, and that the blood sugar values were a rough index of the level of circulating adrenalin.

Finally, a study was made of the effects of blocking the activity of adrenalin. Two sympatholytic agents were tested: Gynergen (ergotamine tartrate) administered in doses of 0.1 cc each containing 5 γ with each injection of adrenalin; and dibenamine in doses of 0.1 cc each containing 1 mg.

It is seen from Table VI that the dose level of Gynergen used was not adequate to block the action of adrenalin or of the intact adrenal medulla. It did, however, suppress hyperglycemia to some extent. Dibenamine, on the other hand, did not affect the usual blood sugar response to adrenalin, but abolished the resistance provided by the latter.

Discussion. The findings indicate that the administration of adrenalin provides substantial protection to adrenalectomized rats against some toxic agents, and that, in the case of KCl and sodium arsenite, the prolongation of life may actually surpass that of intact rats. The production of hyperglycemia is evidently not the mechanism by which the medullary hormone participates in the resistance against these agents; animals treated with adrenalin-antagonists show enhanced susceptibility to intoxication in spite of hyperglycemia.

The relative importance of the adrenal cortex and the medulla in the maintenance of vascular tone is not established. Zweifach, *et al.*(4) obtained in adrenalectomized rats

TABLE VI. Effects of Gynergen and Dibenamine.

No. of inj.	5	6	7	8	9	10	11	12	13	14	15	16	17	Blood sugar, mg %
No. of deaths:					Adrenalectomized rats									
KCl	3		2											120
" + A*							2	1		1	1			200
" + A + G									2	2		1		170
" + A + D			2	1	1	1								230
					Intact rats									
KCl				1		1	2	1						260
" + A										1	1	1	2	360
" + G							3	1	1					190
" + D			1	1	2	1								250

* A = Adrenalin; G = Gynergen; D = Dibenamine.

restoration of the normal state in the vascular bed with cortical steroids. Works of Swingle and others(5,6) point to the role of the cortex in traumatic shock, while Huizenga, *et al.* (7) report on the ineffectiveness of cortical hormones in hemorrhagic shock. Remington (8) found that intact dogs given a large dose of dibenamine succumbed to minor hemorrhages, and that the cardiovascular changes in these animals resembled those of animals in terminal adrenal insufficiency or acute crises following bilateral adrenalectomy. Ramey, *et al.*(9) found that ACE potentiates the blood pressure response to norepinephrine in adrenalectomized dogs. We, however, were unable to confirm this in rats. Fritz and Levine(10) believe that cortical steroids are necessary for the efficient response of blood vessels to sympathin E.

Whatever may be the mechanism, the results obtained by us, together with the observations that adrenalin injection increases the resistance of adrenalectomized animals to histamine(11-13) suggest that at least under the conditions of the present experiments, the presence of the adrenal medulla is of primary importance.

Summary. 1. Administration of adrenalin prolongs survival time of adrenalectomized rats injected with KCl, formaldehyde, and sodium arsenite. 2. Under conditions of our experiments, adrenalin was more effective than cortisone in providing protection against these agents. 3. This protective effect is abolished by simultaneous administration of sympatholytic drugs. 4. The mechanism of protection appears to be through the prevention of vascular collapse. 5. It is suggested that the medullary secretion is an important factor in resisting traumatic shock.

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Studies on Platelets. XVI. Glutamic Oxaloacetic Transaminase Activity of Human Platelets.* (22275)

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Glutamic oxaloacetic transaminase (GOT) is a specific enzyme concerned with the synthesis of glutamic and oxaloacetic acids through the transfer of α-amino nitrogen of aspartic acid to α-ketoglutaric acid. Its presence has been demonstrated in serum of many animals and man, as well as in many animal tissues(1-4). It was observed by Karmen *et al.*(4) that human blood hemolysates

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