EFFECT OF ADRENALECTOMY AND ADRENAL DEMEDULLATION ON CATECHOLAMINE METABOLISM IN RATS

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After adrenalectomy and adrenal demedullation in rats the excretion of dihydroxymandelic acid, of noradrenalin (NA), and (more especially after adrenalectomy) of 3-methoxy-4-hydroxyphenylglycol is increased. Adrenalectomy potentiates the action of reserpine on the NA level in the rats' heart by a greater degree than adrenal demedullation. After adrenalectomy there is no response to intravenous injection of NA as reflected by quickening of the pulse under anesthesia and after administration of cholinolytics. The changes observed indicate acceleration of noradrenalin biosynthesis after adrenalectomy and adrenal demedullation and a disturbance of catecholamine storage, as well as changes in the reactivity of the adrenergic mechanisms of the heart after adrenalectomy.

In order to determine the effect of a deficiency of steroid hormones on catecholamine metabolism it is a sound plan to study changes in the sympathico-adrenal system after adrenalectomy and adrenal demedullation, because, on the one hand, there is a close link between corticosteroids and catecholamine metabolism [3, 5], and on the other hand, certain changes in catecholamine metabolism after adrenalectomy can be attributed to removal of the adrenal medulla [2].

The writers have shown previously that adrenalectomy potentiates the effects of disulfiram and nialamide in the rats' heart, whereas adrenal demedullation does not effect these precesses. This is presumably evidence that noradrenalin (NA) biosynthesis is accelerated in the heart of animals with a deficiency of steroid hormones.

The object of the investigation described below was to study the urinary excretion of three catecholamines (CA), of 3.methoxy-4-hydroxyphenylglycol (MHPG), the combined excretion of metanephrin and

TABLE 1. Excretion (in μg/24 h) of Catecholamines and Their Principal Metabolites in the Urine of Rats after Adrenalectomy and Adrenal Demedullation

Group of animals undergoing	Number of animals	Catecholamines		MHPG	MN + NMN	DHMA
		A	NA			
Mock operation	5	0,40±0,03	0,76±0,11	40±7,1	7,6±1,2	6,2±1,0
Adrenalectomy	4	0	1,12±0,14	68±8,3[1]	6,0±1,5	11,2±2,2*
Adrenal demedullation	5	0,02±0,01	1,2±0,47	54±3,8	7,4±2,6	11±2,2*

*Differences from group of rats undergoing mock operation significant ($P < 0.01$).

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TABLE 2. Effect of Reserpine On Tissue NA Level (in μg/g)

Group of animals	Number of animals	Heart		Cerebral hemispheres	
		control	reserpine	control	reserpine
Intact	8	0,88±0,09	0,39±0,05	0,39±0,02	0,35±0,02
Adrenalectomy	4	0,85±0,14	0,05±0,02	0,40±0,02	0,25±0,03
Adrenal demedullation	5	0,65±0,07	0,17±0,02	0,36±0,03	0,37±0,03

TABLE 3. Changes in Pulse Rate (beats per minute) of Rats Receiving Noradrenalin by Intravenous Injection before and after Melipramine (difference between initial pulse rate and pulse rate 10 sec after NA)

Group of animals	No. of animals	Before injection of melipramine	After injection of melipramine
Intact	5	+64 ± 9	+90 ± 8
Adrenalectomy	5	+ 4 ± 6	+46 ± 5
Adrenal demedullation	5	+48 ± 9	+67 ± 4

normetanephrin (MN plus NMN) and of dihydroxymandelic acid (DHMA), and also to study the functions of storage and absorption of CA after adrenalectomy and adrenal demedullation.

EXPERIMENTAL METHOD

Experiments were carried out on 50 rats of both sexes weighing 150-250 g. Bilateral adrenalectomy and adrenal demedullation were performed as described previously [6]. The rats undergoing the operations received 1% sodium chloride to drink. Reserpine (Rausedil, Richter) was injected subcutaneously in a dose of 0.125 mg/kg 24 h previously. Melipramine (imipramine) was injected intraperitoneally in a dose of 12.5 mg/kg 40 min before the experiments. To study the response of the adrenergic mechanisms of the heart to injection of NA, the compound was injected intravenously in a dose of 20 mg/kg, estimated as base, in 0.85% NaCl solution into rats anesthetized with hexobarbital (50 mg/kg, intraperitoneally), after blocking of the peripheral cholinergic systems by oxyphenonium bromide (2 mg/kg intraperitoneally, 10 min before the NA). The reaction was assessed by the change in pulse rate recorded with an electrocardiograph. The CA concentration in the tissues was determined by Osinskaya's method [4], and in the urine by Baru's method [2], the MHPG concentration was determined by the method of Ruthven and Sandler [16], MN plus NMN by Pisano's method [13], and DHMA by the method of Mijake et al. [11]. Free CA and DHMA and the sum of the free and bound MHPG and methoxycatecholamines were also investigated.

EXPERIMENTAL RESULTS

The results of a study of the excretion of CA and their metabolites in the rats are given in Table 1. After adrenalectomy the largest increase took place in MHPG, the principal end product of CA metabolism in animals of this species [16], which could indicate an increase in the production of NA [18]. This increase was smaller after adrenal demedullation. After both operations the DHMA concentration was increased while that of MN plus NMN was unchanged. The almost total disappearance of adrenalin (A) from the urine after both operations was evidence that its chief source is the adrenal medulla, although a certain quantity of metanephrin was found after adrenalectomy [9]. An increase in the NA excretion was observed after both operations and, in the writers' opinion, like the increase in DHMA excretion it may be due to changes in the storage of CA and their absorption by the tissues.

The decrease in the NA level in the rats' heart under the influence of reserpine was considerably potentiated by adrenalectomy and, to a somewhat smaller degree, by adrenal demedullation (Table 2). After adrenal demedullation in this series, there was a slight decrease in the tissue NA level in the rats' heart, in agreement with results in the literature [8]. The dose of reserpine used caused no changes in the brain of the animals undergoing the mock operation and only slightly reduced the NA in the adrenalectomized rats. Since reserpine is known to block the ability of catecholamine-containing granules in sympathetic neurons to absorb NA [17, 18], this suggests that after adrenalectomy the properties of these

granules in the heart are altered, i.e., that the function of CA storage is modified. According to existing evidence this may be associated with a decrease (adrenalectomy) or an increase (adrenal demedullation) in the intracellular sodium concentration [8, 10].

Results showing the changes in the pulse rate of the rats receiving NA after preliminary administration of hexobarbital and oxyphenonium bromide (without cholinolytics, reflex bradycardia is observed) are given in Table 3. Melipramine, which blocks the absorption of NA by sympathetic nerve endings [18], potentiated the effect of NA. After adrenalectomy there was almost no response to the dose of NA used, but some recovery took place after injection of melipramine. After adrenal demedullation the initial response was unchanged and the effect of melipramine was reduced; it was accordingly concluded that the process of NA absorption in the rats' heart was reduced by this procedure. There are reports in the literature of an increase in the absorption of NA by the isolated heart in adrenalectomized rats [1]. The decrease in response to exogenous CA after adrenalectomy is supported by other findings [14]. It can be concluded from these results that after adrenalectomy there is a marked acceleration of mediator synthesis in the sympathic system, probably due in part to removal of the adrenal medulla [7, 12] and to reciprocal relationships between the medulla and the centers of the sympathico-adrenal system [2], and that it is to some extent the result of a deficiency of steroid hormones. Some changes in catecholamine metabolism after these operations are connected with disturbance of the tissue electrolyte balance (the response to exogenous NA, resistance to reserpine, excretion of NA and DHMA), while the others (absorption of NA) require further research to shed light on their origin.

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