Increase in Noradrenaline Content of Organs after Administration of DOPA in the Cat

L-Noradrenaline has been demonstrated as a normal constituent in most mammalian organs (EULER[1], BACQ and FISCHER[2], SCHMITERLÖW[3], HOLTZ[4]), where its presence is dependent on the adrenergic nerves (GOODALL[5], EULER and PURKHOLD[6]). The amount obtained on extraction of an organ is relatively constant.

It has been suggested that dihydroxyphenylalanine (DOPA) is a precursor of noradrenaline or adrenaline (HOLTZ, HEISE, and LUEDTKE[7], BLASCHKO[8]). HOLTZ, CREDNER, and KOEPP[9], demonstrated that administration of DOPA in man or animals was followed by an increased excretion of its decarboxylation product, hydroxytyramine.

The present report deals with the effect of infusion or injection of various aromatic compounds upon the noradrenaline content of some organ in the cat. The substances used for this purpose have been

dl- and *l*-dihydroxyphenylalanine (DOPA),
l-tyrosine
β-phenylalanine,
hydroxytyramine (HOT),
catechol,
dl-dihydroxyphenylserine (noradrenaline carboxylic acid (DOPS).

The compounds were administered either by slow intravenous infusion or by intramuscular injection in the animal anaesthetized with chloralose. Immediately after the termination of the intravenous infusion and about 1 hour after the intramuscular injection, the animal was killed by air embolism, and the heart, the spleen and the liver were removed and extracted according to EULER[1].

The following table shows the results.

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[6] U. S. VON EULER and A. PURKHOLD, Acta physiol. Scand. *1951* (in the press).
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Cat weight kg		Heart + liver + spleen μg noradr. per kg	Spleen		Heart		Liver	
			μg noradr./ g organ	μg noradr./ kg	μg noradr./ g organ	μg noradr./ kg	μg noradr./ g organ	μg noradr./ kg
2·7	Control	10·6	1·5	2·7	0·8	4·5	0·08	3·4
3·5	Control	7·0	1·5	3·5	0·7	2·8	0·03	0·7
3·3	Control	8·0	1·7	3·4	0·5	1·8	0·12	2·8
3·9	Control	7·0	1·3	3·3	0·6	2·1	0·15	1·6
2·7	Control (no chloralose)	7·9	1·3	2·2	0·5	2·0	0·2	3·7
2·8	HOT 2·9 mg i. v. 60 min.	5·8	0·7	1·1	0·5	2·4	0·1	2·3
1·9	HOT 4·0 mg i. v. 60 min.	5·1	0·0	0·0	0·7	3·1	0·04	2·0
2·3	HOT 10·0 mg i. m.	0·5	0·1	0·2	0·0	0·0	0·01	0·3
2·5	DOPS 10 mg i. v. 60 min.	5·6	0·9	1·5	0·2	1·0	0·13	3·1
2·3	*β*-phenylalanine 20 mg i. v. 46 min.	14·3	1·0	3·9	0·7	3·0	0·2	7·4
2·0	*β*-phenylalanine 20 mg i. m.	4·1	0·4	0·7	0·3	1·0	0·08	2·4
3·4	pyrocatechol 47 mg i. v. 53 min.	10·4	1·1	3·3	1·0	4·6	0·05	2·5
2·8	pyrocatechol 20 mg i. v. 80 min.	5·2	0·6	1·0	1·0	2·7	0·07	1·5
2·6	*l*-tyrosine 10 mg i. v.	13·5	2·5	4·1	0·7	3·3	0·25	6·1
2·6	*l*-tyrosine 10 mg i. v.	14·5	1·5	2·6	1·2	4·8	0·3	7·1
3·1	*l*-tyrosine 20 mg i. m.	7·3	1·5	2·5	0·8	2·2	0·17	2·6
5·6	*dl*-DOPA 32 mg i. v. 3 min. killed, 6 min. later	12·0	0·9	4·1	1·6	5·9	0·25	2·0
3·1	*dl*-DOPA 20 mg i. v. 20 min.	19·2	1·3	4·6	1·0	4·9	0·3	9·7
3·0	*l*-DOPA 5,2 mg i. v. 53 min.	13·3	2·5	4·2	0·75	2·8	0·27	6·3
2·8	*dl*-DOPA 10 mg i. v. 54 min.	15·7	2·2	5·1	1·7	6·5	0·15	4·1
2·8	*dl*-DOPA 10 mg i. v. 62 min.	21·4	3·3	5·4	2·0	7·4	0·6	8·6
3·1	*dl*-DOPA 40 mg i. m.	13·1	2·7	6·3	0·8	3·8	0·11	3·0
2·6	*dl*-DOPA 20 mg i. m.	19·8	2·8	5·9	1·4	5·4	0·35	8·5
3·0	*dl*-DOPA 20 mg i. m.	14·0	3·0	5·0	1·0	3·7	0·2	5·3
2·5	*dl*-DOPA 10 mg i. m.		1·25	3·0	1·0	5·8		
3·0	repeated carotic occlusions 60 min.	5·5	0·8	1·8	0·8	2·9	0·03	0·8
3·2	same, with dl-DOPA 20 mg i. v. 45 min.	8·0	0·8	2·5	0·4	1·3	0·2	4·2

All animals were anaesthetized with chloralose 0·05 g per kg bodyweight after initial ether anaesthesia. Animals receiving preparations intramuscularly were killed 1 hour after the administration of the drug.

From the table it is seen that DOPA in doses of 10 to 40 mg causes a considerable increase in the catechol content of the cat's spleen and heart.

With L-tyrosine, β-phenylalanine and catechol intravenously, relatively high figures were also obtained in some instances. Low figures were noted with HOT and DOPS and also in one experiment with DOPA where repeated carotid occlusions had been made.

Comment

The results reported in the present paper give some support to the findings of ARMAN[1] that DOPA was the only amino acid among several tested which caused an increase in the adrenaline amount of the rat's suprarenals, previously depleted by insulin. The increase in his experiments was not higher than about 30 per cent however, and the total amount never reached the normal figure.

In our experiments the noradrenaline amount in the organs was approximately doubled. The nature of the catechol amine in the organ was checked by paper chromatography which showed spots with the typical position of noradrenaline. It is of interest that dihydroxyphenylserine or dihydroxytyramine did not have this effect under the present experimental conditions. When the former substance was given to rabbits, an increased output of noradrenaline was found in the urine (SCHMITERLÖW[2]).

The results may be explained by the assumption either that DOPA is a precursor of noradrenaline and increases its formation, or of an inhibitory effect of DOPA on the break-down of noradrenaline in the organ. The low figures found after infusion or injection of DOPS or HOT may be explained on the basis of inhibition, such as has been noted for HOT, noradrenaline and related substances on the DOPA-decarboxylase activity in organs by BLASCHKO[3] and by POLONOVSKI, SCHAPIRA, and GONNARD[4].

Samples of dihydroxyphenylserine were kindly placed at our disposal by Dr. H. BLASCHKO, Oxford, and by Hoffmann-La Roche, S. A., Basel.

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Zusammenfassung

Intravenöse oder intramuskuläre Einführung von DOPA in die Katze verdoppelt nahezu den Gehalt an Noradrenalin der Milz, des Herzens und der Leber.

Mit Dihydrooxyphenylserin und Hydroxytyramin wurde dieser Effekt nicht erzielt.

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Action de la surrénalectomie sur les phénomènes thermoanalgésiques provoqués par la cortisone, l'adrénocorticotrophine, le formol, l'adrénaline, la morphine et le pyramidon

Dans une communication antérieure de ce Laboratoire[1], il a été montré que l'acétate de cortisone provoque, chez la souris, une thermoanalgésie significative; les doses efficaces (2,5–12,5 mg/kg, s.c. ou i.p.) étaient égales ou inférieures aux quantités de corticostéroïdes qui sont libérées sous l'effet de l'A.C.T.H. (INGLE, LI et EVANS[1]) ou d'un stress intense (INGLE et NEZAMIS[2]). Des injections répétées d'adrénocorticotrophine eurent un effet similaire et il fut en outre observé que la réactivité à la douleur diminuait après l'application de divers agents qui, entre autres propriétés, ont celle de stimuler le système hypophyso-surrénalien: refroidissement, injections d'acide, de formol, d'adrénaline[3]. On était donc tenté d'envisager une intervention des corticosurrénales dans la genèse de certaines analgésies; il convenait toutefois de contrôler cette possibilité en recherchant l'action de la surrénalectomie sur les effets de différents agents doués de pareilles propriétés.

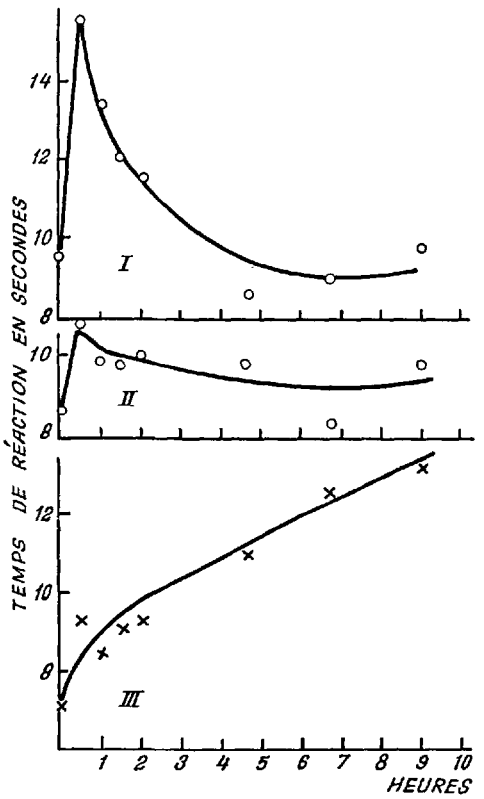

Fig. 1. – Action d'une opération factice et de la surrénalectomie sur l'effet thermoanalgésique de l'adrénaline chez la souris.
I – témoins 1,5 kg/mg d'adrénaline i.p.: 10 animaux.
II – souris opérées 1,5 mg/kg d'adrénaline i.p.: 11 animaux.
III – souris surrénalectomisées 1,5mg/kg d'adrénaline i.p.: 10 animaux.

La méthode de mesure des effets thermoanalgésiques est une variante de celle de WOOLFE et MACDONALD[4], différant de cette dernière par la réaction prise comme test (réflexe de lèchement) et un appareillage adapté à ce réflexe. Les souris étaient, avant toute intervention, triées et entraînées. La surrénalectomie (totale) fut réalisée par voie dorsale sous narcose à l'éther, 24 h avant l'expérience. – Chaque expérience a été réalisée sur au moins dix animaux.

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