shown to be more stimulatory than fresh tumour extracts (9), so the experimental conditions may have been less than optimal to demonstrate maximal stimulation. Any inhibitory effect of local anaesthetic or heparin, or stimulatory effect of possible bacterial antigens on T cell function is eliminated by employing control extracts.

Tumour growth in the presence of tumour-directed immunity remains a paradox. Although experiments involving the culture of human peripheral blood lymphocytes with autologous tumour extracts have, in some reports, demonstrated stimulation only in tumours with a favourable prognosis (10), it seems unlikely that the results we have obtained strongly support the concept of cell-mediated immunity as an important mechanism in limiting tumour spread.

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DOPA in Sympathetic Nerve Tissue—a Possible Source of Serum DOPA in Albino Animals

C. Hansson, J. Poulsen, H. Rorsman and E. Rosengren

Departments of Dermatology and Pharmacology, University of Lund, Lund, Sweden

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Abstract. Dopa, catecholamines, and dopac were determined in superior cervical ganglia of albino rats. The average amount of dopa in ganglia of control animals was 1.1–1.6 μg/g. The concentrations of catecholamines and dopac were similar to values reported by others. The tyrosine hydroxylase inhibitor α-methylparatyrosine methyl ester caused marked decrease in the dopa concentration in the ganglia. The effect of reserpine was less pronounced. The aromatic amino acid decarboxylase inhibitor NSD 1015 markedly increased the dopa concentration.

Key words: Dopa; Dopac; Dopamine; Noradrenalin; Adrenalin; Sympathetic ganglion; Serum; Albino

Recent studies on guinea pigs of different colours suggest that much of the dopa present in the serum originates from the melanocytes (6). Albino animals too have some dopa in the serum. Dopa has been found in the heart, spleen, and a cervical ganglion of guinea pig (1). These findings suggest that sympathetic nerve tissue can store and secrete not only catecholamines but also dopa.

We now report the presence of large amounts of dopa in the superior cervical ganglion of albino rats.

Table I. *Dopa, dopamine (DA), noradrenalin (NA), adrenalin (A), and dopac in the upper cervical ganglia of albino rats*

All values in μg/g. Mean values and ranges are given. (*n*) represents the number of determinations

Treatment (*n*)	Dopa	DA	NA	A	Dopac
None (7)	1.6 0.5–4.8	1.7 0.9–3.2	19 12–33	0.3 0.0–1.4	1.8 1.4–2.1
Saline					
1.5 h (5)	1.5 1.0–2.1	2.5 1.6–3.8	34 25–42	0.3 0.0–1.5	4.0 2.4–6.3
4 h (5)	1.1 1.1–1.2	1.7 1.3–2.1	23 20–26	0.0 0.0–0.0	2.1 1.6–2.7
16 h (5)	1.2 0.9–1.7	2.1 1.7–2.3	27 24–31	0.2 0.0–0.8	3.0 1.7–4.1
Reserpine 5 mg/kg					
4 h (8)	1.1 0.8–1.7	0.6 0.3–0.9	0.4 0.3–0.6	0.0 0.0–0.2	4.1 3.5–4.6
16 h (9)	0.7 0.3–0.8	0.7 0.4–1.2	1.0 0.5–3.7	0.0 0.0–0.1	4.1 3.2–4.6
α-MPT 250 mg/kg					
1.5 h (10)	0.3 0.1–0.7	1.5 0.6–6.5	12 7–16	0.1 0.0–0.9	0.0 0.0–0.0
4 h (5)	1.3 0.5–3.3	0.6 0.3–1.2	6 5.0–7.4	0.0 0.0–0.0	0.0 0.0–0.0
NSD 1015 100 mg/kg					
1.5 h (5)	13 11–16	0.8 0.6–1.0	16 10–25	0.0 0.0–0.0	0.0 0.0–0.0

HPLC was used for determination of dopa, catecholamines, and dopac. Drugs known to influence the metabolism of catecholamines were also studied for their effect on the dopa content in the ganglia.

MATERIAL AND METHODS

Male albino rats (Sprague-Dawley) weighing 230–260 g were used. They were kept on a diet of Ewos Anticimex pellets.

20 control animals were killed without any preceding injections. 6 of these animals were used for determination of dopa in serum. 30 other controls were divided into 3 groups, and were given 0.5 ml of saline intraperitoneally 1.5, 4, or 16 hours before being killed.

The following drugs were used: reserpine, 5 mg/kg body-weight (Serpasil, Ciba); DL-α-methyl-*p*-tyrosine methyl ester HCl, 250 mg/kg body-weight (α-MPT, Labkemi AB, Gothenburg, Sweden); and *m*-hydroxybenzylhydrazine hydrochloride, 100 mg/kg body-weight (NSD 1015, FGA Chemie, Steinheim).

Rats were killed by a blow on the neck and heart exsanguination 4 and 16 hours after intraperitoneal injection of reserpine, 1.5 or 4 hours after injection of α-MPT, and 1.5 h after injection of NSD 1015. The superior cervical ganglia were immediately removed from both sides and extracted with 0.4 M perchloric acid. Serum or ganglia from 2 animals were used for each analysis.

Dopa, dopamine, noradrenalin, adrenalin, and dopac were determined by HPLC and electrochemical detection according to previously described methods (4, 5).

RESULTS

The concentrations of dopa in the three serum samples from 6 control animals were 2.4, 3.8 and 3.8 ng/ml. The results of the analyses of ganglia are summarized in Table I. Control animals had 1.1–1.6 μg dopa per g ganglionic tissue. The concentrations of dopa were similar or lower than those of dopamine and dopac, and 4–8% of those of noradrenalin. The average concentrations of adrenalin were about 1% of those of noradrenalin.

Reserpine diminished the concentrations of catecholamines. The fall in dopa concentrations was less pronounced.

A fall in dopa concentration was noted in animals killed 1.5 h after injection of the tyrosine hy-

droxylase inhibitor α-MPT, but in animals killed 4 h after injection the dopa concentration was normal. The decrease in concentration of catecholamines was more pronounced in animals killed 4 h after injection of α-MPT. Dopac values were 0 in both groups.

The most spectacular effect of the decarboxylase inhibitor NSD 1015 was a marked increase in dopa concentration and a fall in dopac concentration to 0.

DISCUSSION

The finding of large amounts of dopa in the superior cervical ganglion of the rat is of the greatest neurochemical interest. It is generally accepted that tyrosine hydroxylase, the enzyme responsible for dopa formation in neural tissues, regulates catecholamine synthesis (10). The present study has defined the quantity of naturally occurring dopa in a sympathetic ganglion. The amounts of dopa found are remarkably high, and the accumulation mechanism for dopa is probably important in control of neural activity.

Dopa is a key substance in the melanocytes, where the formation of this amino acid is catalysed by tyrosinase. We have recently produced evidence that the serum concentration of dopa in guinea pigs depends on the coat colour, pigmented animals showing higher values than albinos (6). The present findings of large amounts of dopa in the sympathetic nerve system suggest another possible origin of serum dopa, which may explain the presence of dopa in the serum of albino animals with deficient dopa production in the melanocytes. It has been suggested that dopamine in the ganglion is present in small, intensely fluorescent (SIF) cells of a special type (2, 3). The pool of dopa now detected may be localized to such specific cells and/or to the nerve cells.

The pronounced effect of α-MPT on the dopa concentration in the ganglia shows that ganglionic dopa is rapidly released or metabolized.

The half-life of dopamine in ganglia is significantly less than 1 h (7). The rapid rate of dopa and dopamine metabolism suggests that these compounds play an essential role in regulating the function of the sympathetic ganglia. Our findings on catecholamines and dopac conform with the concept, based on neurophysiological and pharmacological studies (8, 9), that dopamine plays an essential part in the sympathetic ganglion.

The sensitive analytical methods used in this study, which allow the determination of dopa, dopamine, and dopac in the amounts present in rat ganglia and in the serum, will undoubtely prove helpful in further elucidating the dopa metabolism of the sympathetic nerve system.

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Influence of Orthostatic Pressure Changes on Blood Flow in Fingers in Generalized Scleroderma

Johannes Kjeldstrup Kristensen

Department of Dermatology, University of Copenhagen, Rigshospital, DK-2100 Copenhagen, Denmark

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Abstract. Autoregulation of blood flow, i.e. tendency towards the maintenance of constant blood flow during changes in arterial perfusion pressure head, has previously been demonstrated in human cutaneous and subcutaneous tissue. The response seem to depend on local intrinsic mechanisms, and the study of autoregulation can yield information as to the reactivity of vascular smooth muscle cells to normal metabolic and myogenic stimuli. Nine patients and 6 normals were studied. Blood flow was measured in subcutaneous tissue of fingers by the local ^{133}Xenon washout technique. A decrease in arterial perfusion pressure head was obtained by graded elevation of the arm above heart level. In 5 normals and 7 patients, blood flow was also measured in a subcutaneous vascular bed made passive by injection of a ^{133}Xenon–papaverine mixture. In this paralysed vascular bed, blood flow diminished corresponding to the decrease in perfusion pressure during elevation of the arm, while in the normal vascular bed blood flow remained almost constant. Patients suffering from generalized scleroderma took an intermediate position. This finding is compatible with an intrinsic vascular smooth muscle cell defect in generalized scleroderma.

In previous studies (8, 9, 10) it was suggested that autoregulation of blood flow was absent from cutaneous and subcutaneous tissue of fingers and cutaneous tissue of hands in generalized scleroderma.

Autoregulation of blood flow, i.e. tendency towards the maintenance of constant blood flow during changes in arterial perfusion pressure has been demonstrated in cutaneous and subcutaneous tissue of normal persons (3, 4, 5). The mechanisms responsible for the adjustment of vascular resistance to changes in arterial perfusion pressure are still largely unknown, but most facts seem to favour a metabolic hypothesis, i.e. vasoactive metabolites liberated from the tissues due to decrease in local oxygyn tension (1, 2).

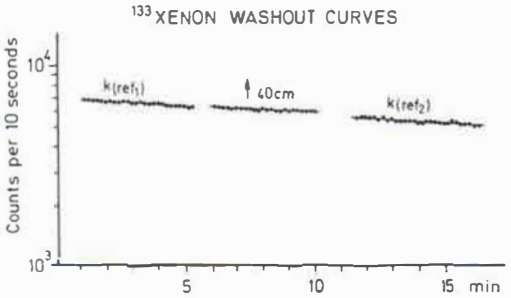

Fig. 1. ^{133}Xenon washout curves illustrationg the triad of measurements.

Autoregulation of blood flow depends on normal functioning of vascular smooth muscle cells. Studies on autoregulation can provide information on the reactivity of vascular smooth mucsle cells to normal metabolic stimuli.

The aim of the present study was to investigate the extent to which the autoregulation of blood flow in fingers is reduced in generalized scleroderma.

METHODS

Blood flow in subcutaneous tissue on the dorsum of the proximal phalanx of the right second finger was estimated by the local ^{133}Xenon washout technique (7, 13). Subcutaneous injection of 0.1 ml ^{133}Xenon dissolved in sterile isotonic saline was performed 30 to 60 minutes before the experiments started in 9 patients and 6 normals. The subjects were seated. A single study consisted of the measurement of ^{133}Xenon washout rate constants (k), (1) with the finger at heart level ($k_{\text{ref. 1}}$); (2) with the finger elevated 20 or 40 cm (k_{test}); and finally (3) with the finger at heart level ($k_{\text{ref. 2}}$)(Fig. 1). In 5 normals and 6 patients, ^{133}Xenon was also administered with an admixture of papaverine (40 mg/ml) to create complete smooth muscle paralysis in the area under study and the sequences were repeated.

The washout rate constant (k) was computed from the logarithmically transformed count rates, corrected for background activity by the least square method.

Relative blood flow during elevation or lowering was computed from the ^{133}Xenon washout rate constants by the formula: $k_{\text{test}}/[k_{\text{ref.1}}+k_{\text{ref.2}}] \cdot \frac{1}{2}$

Statistical tests for significance were performed by using Student's t-test for paired samples and the randomization test for nonpaired samples, 0.05 was chosen as limit of significance.

Patient population and experimental conditions

Informed consent was obtained before each experiment. Patients suffering from generalized scleroderma of the