Der Zusammenhang von MAO-Hemmung und Abschwächung der NA-Wirkung ist nicht klar. Neuere Befunde, wonach die Ansprechbarkeit der Arterienwand von der Konzentration des endogenen NA in der Gefässwand abhängt, bieten eine Erklärungsmöglichkeit. Reserpin, welches den Gehalt von endogenem NA in den Arterien vermindert, erhöht deren Empfindlichkeit auf exogenes NA[11]. Möglicherweise bewirkt IIH Zunahme von endogenem NA in der Gefässwand, wobei im Gegensatz zu Reserpin eine Verminderung der NA-Empfindlichkeit der Aorta zustande kommt.

Im Myokard steigt der Gehalt von endogenem NA nach IIH-Behandlung an[12]. Ferner bewirkt injiziertes NA stärkeren Anstieg dieses Amins im Myokard nach Vorbehandlung mit IIH als ohne Vorbehandlung[13]. Es bleibt noch abzuklären, ob IIH den NA-Stoffwechsel in der Aortenwand in gleicher Weise beeinflusst wie im Herzen.

Verminderte Ansprechbarkeit des Gefäßsystems auf NA könnte das Zustandekommen von orthostatischer Hypotonie beim Menschen während IIH-Behandlung möglicherweise erklären.

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Abteilung für experimentelle Medizin der F. Hoffmann-La Roche & Co. AG., Basel, 6. Mai 1959.

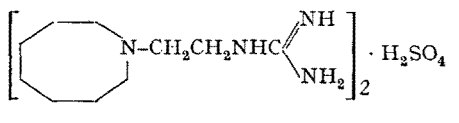
Summary

Twenty hours after pretreatment of rabbits with the monoamine oxidase inhibitor N_2-isopropyl-isonicotinic acid hydrazide (IIH) the norepinephrine induced contraction of the isolated aorta was significantly reduced; the 5-hydroxytryptamine sensitivity could not be changed significantly. Isonicotinic acid hydrazide (INH), a weak monoamine oxidase inhibitor, had no significant effect on the norepinephrine and 5-hydroxytryptamine sensitivity of the aorta.

[11] J. H. Burn und M. J. Rand, Brit. med. J. *1958/I*, 903; J. Physiol. *144*, 314 (1958).
[12] A. Pletscher, Exper. *14*, 73 (1958).
[13] A. Pletscher und K. F. Gey, in Vorbereitung.

[2-(Octahydro-1-azocinyl)-ethyl]-guanidine sulfate (CIBA 5864-SU), a New Synthetic Antihypertensive Agent

SU-5864, which is [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate has been studied to ascertain its antihypertensive properties in animals:



$7^1/_2$ to 15 mg/kg intravenously of SU-5864 markedly lowered the arterial pressure of unanesthetized renal and neurogenic hypertensive dogs while its effects on the arterial pressure of the unanesthetized normotensive dog were slight. In the anesthetized normotensive dog SU-5864 inhibited carotid occlusion reflex pressor responses and antagonized the severe pressor responses elicited by high doses of amphetamine.

Marked delayed relaxation of the nictitating membranes of dogs and cats was produced by 10 to 15 mg/kg SU-5864 intravenously. As demonstrated in the cat this relaxation was associated with a blockade of transmission somewhere in the cervical sympathetic trunk-smooth muscle complex, such that the nictitating membranes could not be retracted by preganglionic faradization. Except for a very transient period SU-5864 did not interfere with transmission across the superior cervical ganglion nor with the conduction along pre- or post-ganglionic nerve fibers. However, at the same time that the nictitating membranes could not be retracted by nerve stimulation, they were demonstrated to be hypersensitive to injected norepinephrine. From these data we infer that SU-5864 must produce an inhibition of the release and/or distribution of transmitter substances from sympathetic nerve terminals.

The effects described above last for periods ranging from 5 to 20 days following a single intravenous administration of SU-5864.

A convenient method of preparation utilized octahydroazocine[1] as starting material. Treatment with chloroacetonitrile gave the octahydro-1-azocineacetonitrile, b.p. 114–118°C/14 mm; $n_D^{24} = 1{\cdot}4720$; calculated for $C_9H_{16}N_2$: C 71·11; H 10·61; N 18·43; Found: C 71·17; H 10·62; N 18·36. Lithium aluminium hydride reduction of the nitrile yielded octahydro-1-azocineethylamine, b.p. 108–111°C/14 mm; $n_D^{22} = 1{\cdot}4830$; calculated for $C_9H_{20}H_2$: C 69·29; H 12·92; N 17·96; Found: C 69·26; H 12·94; N 17·89. Reaction of the amine with S-methylisothiourea sulfate resulted in the formation of the above described SU-5864 which was recrystallized from aqueous ethanol and melted with decomposition at 276–281°C; calculated for $(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$: C 48·55; H 9·37; N 22·65; S 6·48; Found: C 48·49; H 9·51; N 22·49; S 6·33.

R. A. Maxwell, R. P. Mull, and A. J. Plummer

Research Department, CIBA Pharmaceutical Products Inc., Summit (New Jersey), May 4, 1959.

Résumé

On décrit la chimie et la pharmacologie d'un nouvel agent antihypertenseur.

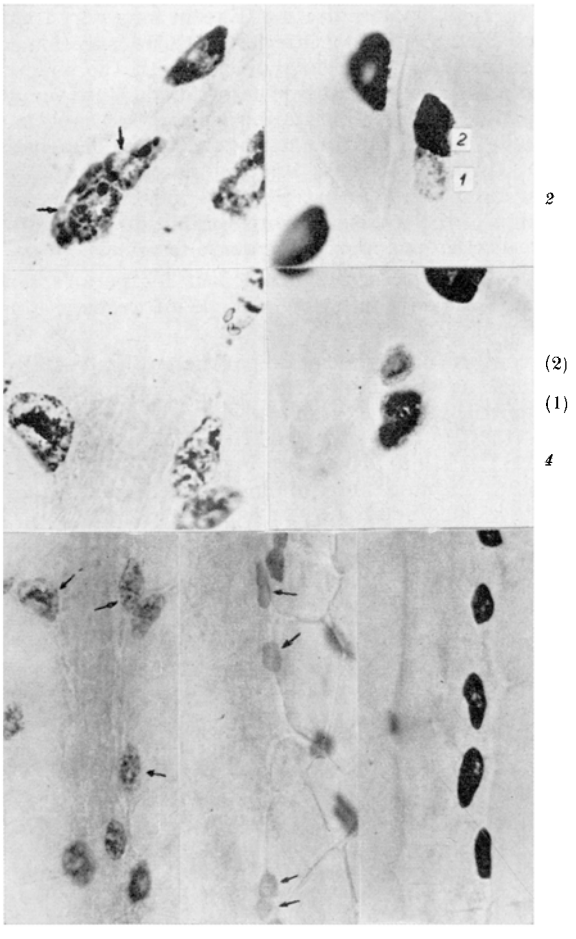
[1] F. F. Blicke and N. J. Doorenbos, J. Amer. chem. Soc. *76*, 2317 (1954).

On the Relation between the Secretion of the Perivascular Mast Cells and the Serum Level of Mucoproteins

The mast cells are well known as producers of histamine, 5-hydroxytryptamine, heparin, and hyaluronic acid[1]. We have already demonstrated their secretory changes under experimental conditions[2–4] resulting in a heparinemia[5–8]

[1] G. P. Fulton, F. L. Maynard, J. F. Riley, and G. B. West, Physiol. Rev. *37*, 221 (1957).
[2] M. Hill, Nature *180*, 654 (1957).
[3] M. Hill and M. Praslička, Acta haemat. *19*, 278 (1958).
[4] M. Hill, Acta anat. *35*, 118 (1958).
[5] H. Engelberg, Proc. Soc. exp. Biol. Med., N. Y. *97*, 304 (1958).
[6] J. G. Allen, M. Sanderson, M. Milham, A. Kirschon, and L. O. Jacobson, J. exp. Med. *87*, 71 (1948).
[7] R. J. Havel and E. Boyle, Proc. Soc. exp. Biol. Med., N.Y. *85*, 468 (1954).
[8] R. P. White and P. H. Woodard, Amer. J. Physiol. *188*, 189 (1957).

or in an increased serum polysaccharide level[9]. From these observations, a more general suggestion could be deduced, including the relation of mast cell secretion to the serum level of hexosamine containing compounds, such as mucoproteins.



The microphotographs illustrate the perivascular mast cells of the mesentery after toluidine blue staining.

Fig. 1.—3 h after injection of cortisol in adrenalectomized rat. Metachromatically stained vacuoles in mast cells of lymphatic adventitia. Here and there (↗) loss of stainability of granules. × 660.

Fig. 2.—3 h after injection of cortisol in adrenalectomized rat. Loss of granule stainability in mast cell (1) of lymphatic adventitia. In the cytoplasm there are sporadic small, metachromatically stained droplets. The mast cell in close vicinity (2) is still intact. × 660.

Fig. 3.—24 h after injection of formaldehyde in normal rat. Partial lysis in mast cells of arteriole adventitia. In the cytoplasm only a metachromatically stained network remains. × 660.

Fig. 4.—24 h after injection of formaldehyde in adrenalectomized rat. Beginning of total lysis of mast cell granules (1) in arteriole adventitia. Around the cell a metachromatically stained halo is visible. In the mast cell in close vicinity (2) the total lysis of granules is already complete. × 660.

Fig. 5.—24 h after injection of formaldehyde in adrenalectomized rat. Partial lysis in mast cells (↗) of arteriole adventitia. × 380.

Fig. 6.—24 h after injection of cortisol in adrenalectomized rat. Loss of granule stainability in mast cells (↗) of lymphatic adventitia. × 380.

Fig. 7.—Normal mast cells of lymphatic adventitia in adrenalectomized control rat six days after adrenalectomy. × 380.

[9] B. SHACTER, H. SUPPLEE, and C. ENTENMAN, Amer. J. Physiol. *169*, 508 (1952).

	0 h	24 h	48 h
Formol stress in normal rats	24 ± 2·7	43 ± 12·5 §	36 ± 2·6§
Cortisol in normal rats .		31 ± 2·6*	29 ± 1·5
Formol stress in adrenalectomized rats . . .	28·2 ± 3·7	43 ± 6·1§	40·2 ± 7·9
Cortisol in adrenalectomized rats . . .		46·5 ± 5·5§	56 ± 6·0§

The values of serum mucoproteins expressed in relative thymol units. * $p < 0{\cdot}05$; § $p < 0{\cdot}02$.

An increase of serum mucoproteins was achieved by stress[10] elicited either by a single intramuscular injection of 0·3 ml/100 g of 4% formaldehyde, or by an intramuscular injection of 4 mg/100 g cortisol (Scheroson *F* «Schering») in normal and in adrenalectomized rats, six days after adrenalectomy. 84 male Wistar rats including the controls, were used; they were, 3–5 months old, their body weight were 180–220 g. The rats were killed by decapitation 3, 6, 12, 24, 48 h after injection. Specimens of the mesentery and omentum maius were prepared in a standard manner[4]. The values of serum mucoproteins were determined by the turbidimetric method[11] in relative «thymol units» by means of the barium sulphate standard[12], applying the Clett-Summerson electrophotometer. The determination of the leucocyte and eosinophil number and of the leucocyte differential count, always prior to treatment and in killing, enabled an orientation as to the course of stress.

In mast cells of the lymph vessel and the arteriole adventitia, two types of secretion changes can be distinguished:

1. Intracellular formation of metachromatically stained vacuoles (Fig. 1) accompanied by swelling and decrease or even loss of stainability of the granules (Fig. 2).

2. Partial (Fig. 3) and total (Fig. 4) lysis of granules, identical with those which were found during the shock[4], accompanied by shrinkage of granules.

In the course of formaldehyde stress, both types of secretory changes developed. During the decrease of lymphocytes and eosinophils, i. e., in the glucocorticoid phase of stress, the formation of vacuoles took place; subsequently, during the mineralocorticoid phase (24 to 48 h)[13], lysis of granules occured. In the adrenalectomized rats, however, there was no formation of vacuoles, but in all stages of stress only lysis of granules occured, with a maximal incidence 24 h after formaldehyde injection (Fig. 5). On the other hand, in adrenalectomized cortisol-treated rats only vacuoles were formed accompanied by swelling and loss of granule stainability. The vacuoles appeared already 3 h after injection; stainability of granules was decreased to a minimum after 24 h (Fig. 6). Even after 48 h, the granules of the perivascular mast cells

[10] D. S. KUSHNER, K. HONIG, A. DUBIN, H. A. DYNIEWICZ, D. BRONSKY, J. DE LA HUERGA, and H. POPPER, J. lab. clin. Med. *47*, 409 (1956).

[11] J. DE LA HUERGA, A. DUBIN, D. S. KUSHNER, H. A. DYNIEWICZ, and H. POPPER, J. lab. clin. Med. *47*, 403 (1956).

[12] R. E. SHANK and C. L. HOAGLAND, J. biol. Chem. *162*, 133 (1946).

[13] M. HILL, K. DVOŘÁK and M. POSPÍŠIL, Nature (in press).

had remained almost unstained. Equal but less intensive was the effect of cortisol in normal rats.

In the early stages, the reactions of the perivascular mast cells were, in all experimental groups, accompanied by those of the extravascular mast cells; but at 24 and 48 h the reaction was almost exclusively limited to the perivascular mast cells.

The statistically significant serum mucoprotein elevation was attained in all four groups of animals at 24 h after injection (Tab.).

Discussion. In addition to the opinions hitherto expressed[14,15,1], we believe that we may infer from our results that mast cells, besides their tissue function that can be said to be a local one, also exercise a system function by secreting substances of mucopolysaccharide nature into the circulation. Two types of morphological (secretory) changes suggest that there are at least two types of substances secreted, i. e., nonsulphated mucopolysaccharide of hyaluronate nature and sulphated mucopolysaccharide related to heparin[2–4,16]. At present, it is not possible to decide whether the secretory changes in the perivascular mast cells are the cause of, or the reaction to, the increased serum mucoproteins. Both phenomena, i.e., the mucoprotein rise[17] and the changes in the mast cells are, generally, independent from the adrenal. The demonstrated dependence of the secretion of the hyaluronate type on the adrenals indicates, however, that the adrenals are concerned with the mucopolysaccharide patterns secreted by mast cells.

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Institute of Biophysics, Czechoslovak Academy of Sciences, Brno, March 3, 1959.

Zusammenfassung

Es wurden bei den mit Formaldehyd oder Cortisol belasteten Ratten Sekretionsvorgänge adventitialer Mastzellen beobachtet, und zwar zur Zeit des Ansteigens der Serummukoproteine. Die Beziehungen zwischen beiden Phänomenen wurden besprochen.

[14] G. Asboe-Hansen, Internat. Rev. Cytol. *3*, 399 (1954).
[15] J. F. Riley, Pharmacol. Rev. *7*, 267 (1955).
[16] M. Hill, Exper. *13*, 395 (1957).
[17] N. F. Boas and J. B. Foley, Endocrinology *56*, 305 (1955).

Die Bedeutung konstanter Temperaturbedingungen für ERG-Untersuchungen bei Kleinsäugern

Grösse und Verlauf des Elektroretinogramms (ERG) werden durch verschiedene Versuchsbedingungen beeinflusst, von welchen neben den Reizparametern vor allem der Adaptationszustand die notwendige Beachtung findet, während die Temperatur des untersuchten Auges meist nicht kontrolliert wird. Da insbesonders bei narkotisierten Kleinsäugern mit einer beträchtlichen Auskühlung zu rechnen ist, kann eine Vernachlässigung des Temperaturfaktors schwerwiegende Messfehler verursachen.

Als Versuchstiere dienten 15 Albinoratten (männlich, 190–260 g). Die Tiere wurden 2 h vor dem Versuch narkotisiert (0,12 g/100 g Urethan intraperitoneal) und ihre Körpertemperatur bis zum Versuchsbeginn konstant gehalten (Thermostat oder Strahlungsheizung). Die rektale Messung der Kerntemperatur erfolgte mittels Cu-Konstantan-Thermoelement und Lichtzeigergalvanometer, ferner wurde in einigen Versuchen die Temperatur des linken Auges mit einem retrobulbär eingeführten feinen Thermoelement kontrolliert. Das ERG des atropinisierten und durch Lidsuturen weit geöffnet gehaltenen rechten Auges wurde mit einer durch die Cornea geführten Ag-AgCl-Drahtelektrode (0,1 mm ⌀) gegen eine paraorbitale gleichartige Bezugselektrode abgeleitet und mit Gleichstromverstärker (Tönnies), Doppelstrahl-KSO und Camera

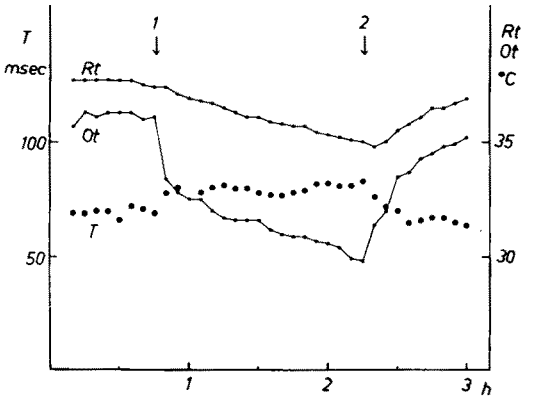

Abb. 1. Verlauf von Rektaltemperatur (*Rt*), Orbitaltemperatur (*Ot*) und Gipfelzeit der *b*-Welle (*T*) bei einem Versuchstier mit Thermoisolation von Rumpf und Extremitäten. Raumtemperatur 17 C. Zwischen 1 und 2 Strahlungsheizung ausgeschaltet. Maximale Reizintensität (100%), Helladaptation an 16 lux.

(Recordine, Tönnies) aufgenommen. Der zweite Strahl des KSO diente zur Registrierung des Lichtreizes (Reizfeld 30 cm vor dem Auge, 3 cm ⌀; Leuchtdichte maximal $3 \cdot 10^4$ cd/m² = 100%, abstufbar durch Neutralfilter; Reizdauer 25 ms). Die Temperatur des Untersuchungsraumes lag in den verschiedenen Versuchen zwischen 16,5 und 18°C, wobei ein Ventilator für konstante Luftbewegung sorgte. Über dem Tier war ein Infrarotstrahler angebracht, mit welchem das Tier erwärmt bzw. auf konstanter Temperatur gehalten werden konnte. In 3 Ver-

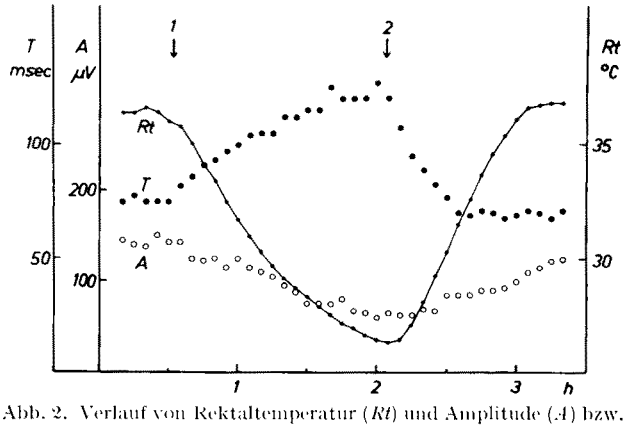

Abb. 2. Verlauf von Rektaltemperatur (*Rt*) und Amplitude (*A*) bzw. Gipfelzeit (*T*) der *b*-Welle bei vorübergehender Abschaltung der Strahlungsheizung (1: Heizung ausgeschaltet, 2: Heizung eingeschaltet). Maximale Reizintensität (100%), Helladaptation. Gleicher Versuch wie Abb. 1.

suchen wurde die Wärmeabgabe des Tieres durch Einhüllen von Rumpf und Extremitäten in Watte und wärmeisolierende Tücher reduziert. Die Versuche wurden teils bei Dunkeladaptation (Beginn nach 2 h Dunkelaufenthalt), teils bei mässiger Helladaptation (6–16 lux an Stelle des