microsome, at the enzyme or at the exit from the microsome.

Isonicotinic acid does not alter the rate of bilirubin formation. Phenelzine and isocarboxazid decrease the rate of conjugation of bilirubin in slices and the effect could be explained by enzyme inhibition. The stimulation of bilirubin conjugation in slices by iproniazid and nialamide and the inhibition of conjugation in homogenates is more difficult to explain. It may be that the drug facilitates the passage of bilirubin through the slice to the enzyme site, a process which it cannot do in homogenates. An alternative explanation is that since the relationship between enzyme inhibition and stimulation is so close, conditions in the slice may facilitate enzyme stimulation rather than enzyme inhibition.

The experiments show that the tranferase conjugating *o*-aminophenol is usually inhibited whereas the effect of the drugs on bilirubin conjugation is variable. Since the liver slice more closely resembles the intact liver rather than the homogenate preparations the cause of monoamine oxidase inhibitor jaundice cannot be explained on inhibition of bilirubin glucuronyl transferase alone. The process causing the jaundice is probably complex and it may be that formation of hepatotoxic intermediaries by metabolism of the drug in the endoplasmic reticulum may play a part as well as possible alterations in cell permeability and an effect on the enzyme[6].

Zusammenfassung. Die Wirkung von Monoamino-Oxidase-Blockern in Verbindungen ist in vitro veränderlich und hängt vom benutzten Substrat und Gewebe ab. Im allgemeinen wird die *o*-Aminophenol-Verbindung blockiert, während die Bilirubinverbindung verhindert oder auch angeregt werden kann. Die verschiedenen Wirkungen können von Variationen von der Verfügbarkeit des Substrats für die Enzyme abhängen. Es ist sehr unwahrscheinlich, dass die Monoamino-Oxidase-Blocker-Gelbsucht aus der Blockierung der Glucuronyl-Transferase allein zu erklären ist.

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Norepinephrine Depleting and Antihypertensive Effect of 4-Methoxy-3,5-dihydroxyphenylalanine

Amongst several amino acids studied as potential metabolic precursors of false adrenergic transmitters, 5-hydroxydopa (5-HO-dopa) was found to induce a marked norepinephrine depletion in peripheral sympathetically innervated organs of various species[1]. Adrenergic transmission in cats pretreated with 5-HO-dopa was greatly impaired[1,2]. 5-Hydroxydopamine and its O-methylated and/or β-hydroxylated metabolites were found to be stored in adrenergic nerves and liberated as false adrenergic transmitter substances[1-3].

In the course of further studies the para-O-methylated derivative of 5-HO-dopa proved to be an even more potent depletor and showed interesting antihypertensive properties in renal hypertensive rats.

The norepinephrine depleting action of 4-methoxy-3,5-dihydroxyphenylalanine was studied in rats which were pretreated with either 100, 50, 25 or 12.5 mg/kg 20 and 4 h before sacrifice. The compound was given as aqueous suspension by stomach tube. The norepinephrine content of heart and brain was determined according to the method of BERTLER et al.[4]. The norepinephrine values are expressed in % of control values obtained in rats which were given saline instead of the drug.

As shown in the Table, there is a clear-cut dissociation between the norepinephrine depleting effect in brain and heart. The dissociation seems to be somewhat smaller than in the case of 5-HO-dopa. However, at the doses used in these experiments the animals showed no noticeable changes in gross behaviour, especially no sedation.

In a second series of experiments the effect of pretreatment with 4-methoxy-3,5-dihydroxyphenylalanine on the blood pressure of renal hypertensive rats was studied. Systolic blood pressure was measured according to the method described by GEROLD et al.[5]. After 3 control days the rats were given 100 mg/kg twice daily for $2^1/_2$ days (a total of 5 doses) either by stomach tube or i.p. As shown in the Figure, 4-methoxy-3,5-dihydroxyphenylalanine markedly reduced the elevated blood pressure both after oral and i.p. administration.

In experiments with isolated perfused spleens of pretreated cats the norepinephrine output and the contractile response to sympathetic nerve stimulation were greatly reduced and 4-methoxy-3,5-dihydroxyphenethylamine was liberated as a false sympathetic transmitter. The detailed results of these experiments will be published elsewhere.

The effect of 4-methoxy-3,5-dihydroxyphenylalanine on the norepinephrine content of heart and brain of the rat

Doses of 4-methoxy-3,5-dihydroxyphenylalanine[a]	% Controls	
	Heart	Brain
2 × 100 mg/kg	2.8 ± 1.4	26.6 ± 2.2
2 × 50 mg/kg	13.5 ± 2.1	36.2 ± 2.5
2 × 25 mg/kg	45.7 ± 7.8	67.0 ± 3.0
2 × 12.5 mg/kg	55.8 ± 7.5	80.5 ± 4.2

[a] The single doses were given by stomach tube 20 and 4 h before sacrifice.

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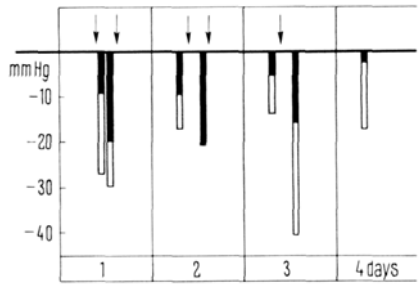

Changes in systolic blood pressure of hypertensive rats treated with 4-methoxy-3,5-dihydroxyphenylalanine. Open columns represent i.p., filled columns oral treatment. A total of 5 doses of 100 mg/kg was given over $2^1/_2$ days. The initial blood pressure of the oral group was 170 ± 3.6 mm Hg ($n = 5$), of the i.p. group 208 ± 2.9 mm Hg ($n = 5$). Pressure changes greater than 10 mm Hg are statistically significant ($p < 0.05$).

In conclusion our results demonstrate 4-methoxy-3,5-dihydroxyphenylalanine to be a precursor of a false adrenergic transmitter with antihypertensive properties in renal hypertensive rats.

Zusammenfassung. 4-Methoxy-3,5-dihydroxyphenylalanin, die metabolische Vorstufe eines «falschen» sympathischen Transmitters, bewirkt an renal-hypertonen Ratten sowohl bei intraperitonealer als auch bei oraler Verabreichung eine Senkung des Blutdrucks. Bei fehlender Sedation wird der Noradrenalingehalt im Gehirn weniger stark gesenkt als im Herzen.

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Department of Experimental Medicine, F. Hoffmann- La Roche & Co. Ltd., Basel (Switzerland), 22 November 1967.

Electron Microscopy of Medial Lemniscal Terminal Degeneration in the Ventral Posterolateral Thalamic Nucleus of the Cat

The results presented in this note are part of an anatomical study of the thalamic termination of the classical spino-thalamic, the dorsal column-medial lemniscus and the cervico-thalamic systems in the cat. That the dorsal column nuclei (DCN) project via the medial lemniscus to the contralateral ventral posterolateral thalamic nucleus (VPL) is well known[1]. The cervico-thalamic system takes its origin in the lateral cervical nucleus (LCN) in the first and second cervical segments of the spinal cord. The axons cross to the contralateral anterior funiculus to travel in the dorsolateral part of the medial lemniscus to the thalamus[2]. Using light microscope techniques we have found preterminal degeneration in the contralateral VPL after unilateral lesions confined to the LCN (Boivie and Grant, to be published). By electrophysiological technique, the same site of termination has been found for the cervico-thalamic system[3]. The third system, the classical spino-thalamic, will not be dealt with here.

In a series of adult cats unilateral lesions of the DCN and the LCN, respectively, were made. The cats were perfused with buffered formalin according to a method described previously[4]. The lesions were cut in serial sections which were stained alternately with thionin and according to van Gieson. For this electron microscope investigation 2 cases with a post-operative survival period of 5 days were selected. One had a complete lesion of the DCN and the other an almost complete lesion of the LCN.

The contralateral VPL was dissected free and prepared for thin sectioning according to a method described before[4].

Degenerating terminal boutons were seen in both cases and the degeneration was of the electron dense type[5]. In the case with the DCN lesion, most of the degenerating terminal boutons were observed in synaptic contact with dendritic shafts (Figure 1), but some were in contact with cell bodies (Figure 2). The degenerating boutons were about 1 μ in diameter, were very electron dense and surrounded by normal boutons. The nerve cells contacted by the degenerating boutons seemed to be rather small, about 20 μ in cross-sectional diameter, while the dendrites contacted by the boutons were of different sizes.

In the case with the LCN lesion the degenerating terminal boutons were also found in contact with both dendritic shafts and cell bodies; most frequently, however, with the former. The degenerating boutons were of the

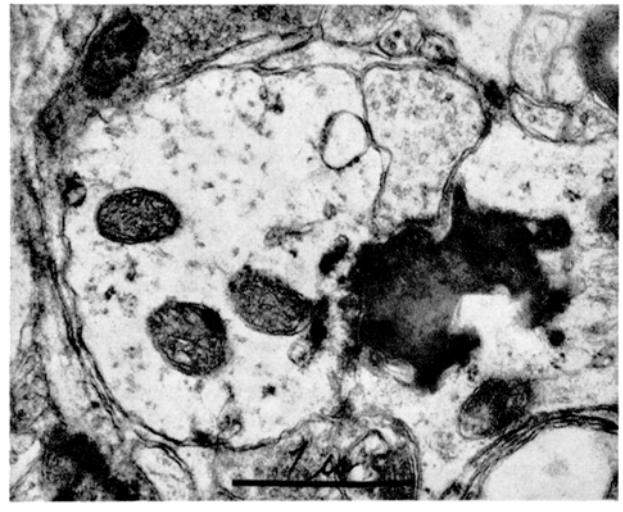

Fig. 1. Degenerating terminal bouton in the VPL 5 days after lesion of the DCN on the contralateral side. The bouton is situated on a medium sized dendrite. × 23,000.

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