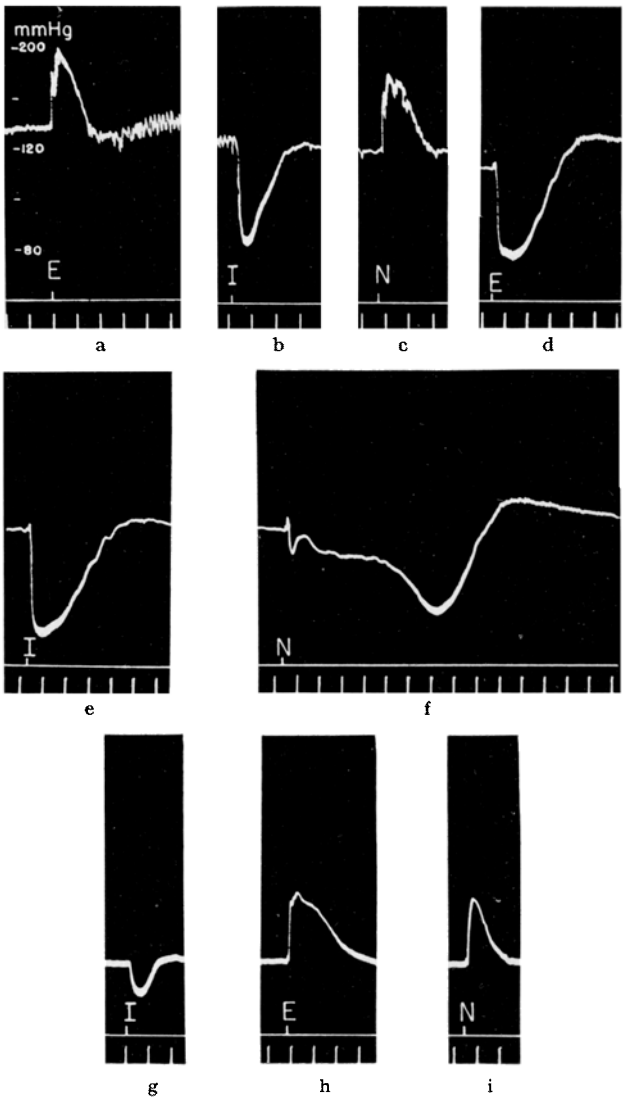

Recording of the carotid arterial blood pressure of a 8·4 kg male dog anesthetized with 30 mg/kg sodium pentobarbital (Nembutal) intravenously. E. l-epinephrine bitartrate, 5 μg/kg. I. l-isoproterenol hydrochloride, 5 μg/kg. N. l-arterenol bitartrate hydrate, 5 μg/kg. Between C and D the animal received 2 intravenous injections of 5 mg/kg of dibenzyline hydrochloride. Between F and G the animal received 3 slow intravenous injections (over a 5 min period) of 5 mg/kg of dichloroisoproterenol hydrochloride (DCI). All drugs were washed in with 3 ml of normal saline. Time markings represent 1 min intervals. 90 min had elapsed between C and D and 110 min between F and G.

blockade by DCI is at present unknown; there is the possibility that the blocking agents are displaced from the excitatory receptors by DCI, permitting their accessibility to the pressor amines. On the other hand, DCI may, by blocking only inhibitory receptors, permit a greater concentration of the injected catecholamines to overcome an incomplete block of the excitatory receptors. Studies are in progress to determine the mechanism of these interesting observations.

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Zusammenfassung

Mit Dibenzylin vorbehandelte anästhetisierte Hunde reagierten nach Dichloroisoproterenol(DCI)-Verabreichung sofort mit «Pressor response» auf Epinephrin und Norepinephrin. Ähnliche Befunde ergaben sich auch bei adrenergischer Blockade mittels Dihydroergotamin oder Benzodioxan.

The Differences in the Accumulation and Metabolism of Catechol Amines in Heart and Liver[1]

It is known that monoamine oxidase and O-methyl transferase are responsible for the inactivation of catechol amines *in vivo*. However the importance of monoamine oxidase relative to O-methyl transferase in the inactivation of the catechol amines in various tissues is unknown. It is possible that in each organ the action of one or the other enzyme predominates. The present study shows that there are differences in the extent to which the catechol amines are inactivated by monoamine oxidase and O-methyl transferase in heart and liver.

10 ml of $4{\cdot}5 \times 10^{-6}$ solution of norepinephrine-7-H^3 and epinephrine-1-C^{14} with an H^3:C^{14} ratio of 5:1 was infused for 30 min into the femoral vein of untreated and iproniazid-treated cats. Immediately after killing, various organs were removed, homogenized in saline, and then deproteinized with perchloric acid. The extracts of each organ were separated into catechol amine, methoxy catechol amine, and acidic-neutral fractions[2]. The catechol amine fraction after acetylation, was submitted to paper chromatography[3] and the radioactivity was found to be associated with unchanged norepinephrine and epinephrine. The methoxy catechol amine fraction was also acetylated in the same manner and it was shown by paper chromatography that the radioactivity is associated with 3-methoxy norepinephrine and 3-methoxy epinephrine. The acidic-neutral fraction was chromatographed in two different solvent systems[4] and the mobilities of the radioactive zones were identical with 3,4 dihydroxy mandelic acid, 3-methoxy 4-hydroxy mandelic acid, and 3-methoxy 4-hydroxy phenyl glycol.

The H^3 and C^{14} activities of acetylated norepinephrine, epinephrine, 3-methoxy norepinephrine, and 3-methoxy epinephrine obtained after paper chromatography are presented in Table I. The presence of tritium in the epinephrine and 3-methoxy epinephrine zones indicates that norepinephrine is converted into epinephrine in these organs. The absence of C^{14} in the norepinephrine zone in these organs shows that epinephrine is not demethylated to norepinephrine and that N-methylation of norepinephrine to epinephrine is an irreversible process.

A comparison of the activities of the catechol amine, methoxy catechol amine, and acidic-neutral fractions is presented in Table II. The high activity of the acidic-neutral fraction of the heart shows that the catechol amines are, to a large extent, metabolized by monoamine oxidase in the heart. In contrast to such organs as liver, spleen, kidney, and adrenal glands, which accumulated infused norepinephrine and epinephrine in both un-

[1] This investigation supported by grants from Nat. Inst. Health, and presented in part to Fed. Amer. Soc. for exp. Biol., Chicago, April 1960.

[2] M. Goldstein *et al.* *16*, Exper. 211 (1960).

[3] M. Goldstein *et al.*, Exper. *15*, 80 (1959).

[4] M. Goldstein *et al.*, Biochim. biophys. Acta *33*, 572 (1959).

Table I. The H^3 and C^{14} activities of norepinephrine, epinephrine, 3-methoxynorepinephrine, and 3-methoxyepinephrine isolated from heart and liver by acetylation technique and paper chromatography.

Compound	Heart C. p. m. × 10^2 per 1 g tissue				Liver C. p. m. × 10^2 per 1 g tissue			
	H^3		C^{14}		H^3		C^{14}	
		Ipr.[a]		Ipr.		Ipr.		Ipr.
N, O, O-triacetyl norepinephrine	0	5·6	0	0	1·4	3·1	0	0
N, O, O-triacetyl epinephrine	0	0·05	0	0·17	0·03	0·2	0·14	0·35
N, O-diacetyl 3-methoxy norepinephrine	13	22	0	0	12	57	0	0
N, O-diacetyl 3-methoxyepinephrine	0·8	0·6	4·1	8·0	0·3	0·8	4·7	16

[a] Cats treated 6 h prior to infusion with 100 mg/kg Iproniazid.

Table II. The distribution of H^3 and C^{14} in different fractions of heart and liver after an intravenous infusion of norepinephrine-7-H^3 and epinephrine-1-C^{14} (the H^3:C^{14} ratio of the infused solution was 5:1).

Fraction	Heart C. p. m. × 10^2 per 1 g tissue				Ratio		Liver C. p. m. × 10^2 per 1 g tissue				Ratio	
	H^3		C^{14}		H^3:C^{14}		H^3		C^{14}		H^3:C^{14}	
		Ipr.[a]		Ipr.		Ipr.		Ipr.		Ipr.		Ipr.
Catechol amines	0	8·0	0	0·5	—	16	2·4	5·0	0·12	0·23	20	22
Methoxycatechol amines	16·6	24·5	5·8	8·1	2·8	3·1	18·0	60·0	5·6	20·0	3·2	3·1
Acidic-Neutral	17·0	6·8	5·5	2·5	3	2·7	8·2	5·5	3·9	2·4	2·1	2·3

[a] Cats treated 6 h prior to infusion with 100 mg/kg Iproniazid.

treated and iproniazid-treated cats[5], the heart accumulated these compounds only in iproniazid-treated cats. While no unmetabolized catechol amines are found in the hearts of untreated cats, in the treated cats there is an even greater accumulation than in the liver. This indicates that monoamine oxidase inhibitors allowed exogenously infused norepinephrine and epinephrine to accumulate in the heart and therefore demonstrates the importance of this enzyme in the metabolism of the catechol amine in the heart. On the other hand, the activity of the methoxy catechol amine fraction in the heart increases only 1·5–2 times more in the iproniazid-treated cats than in the non-treated cats, while in the liver the activity increases 3–4 times. This demonstrates that O-methyl transferase is relatively less active in the heart than in the liver.

The H^3:C^{14} ratio in each fraction was calculated and is presented in Table II. In the catechol amine fraction of the normal as well as the iproniazid-treated cats, the H^3:C^{14} ratio in the catechol amine fraction was greatly increased as compared with the infused solution. Since norepinephrine was infused as H^3, this higher ratio shows that norepinephrine remains intact to a greater extent than epinephrine. The methoxy catechol amine and the acidic-neutral fraction shows a marked decrease in the H^3:C^{14} ratio as compared with the infused solution. This shows that epinephrine is more rapidly metabolized *in vivo* than norepinephrine in both heart and liver.

The more rapid metabolism of epinephrine compared with norepinephrine may be the result of the faster disappearance of epinephrine from the circulation[6,7]. Other possible factors are competition between norepinephrine and epinephrine for the inactivating enzymes and differences in binding properties of these two compounds.

This study demonstrates that catechol amines in the heart are metabolized to a greater extent by monoamine oxidase than by O-methyl transferase. On the other hand in the liver O-methyl transferase seems to be the enzyme primarily responsible for the inactivation of catechol amines. The role of iproniazid in the accumulation of catechol amines in the heart is of special interest because iproniazid has been shown to be useful in the treatment of angina pectoris. The increase of catechol amine in the heart may lead to coronary dilation[8] and this may explain the effect of iproniazid on angina pectoris.

Other organs have also been investigated and a full report will be published elsewhere.

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N. Y. U. School of Medicine, New York, and Seton Hall College of Medicine, Jersey City (N. J.), May 16, 1960.

Zusammenfassung

Noradrenalin und Adrenalin werden von Katzen nach simultaner intravenöser Darreichung zum Teil unverändert in der Leber und anderen Organen gespeichert, jedoch nicht im Herzen. Nach Vorbehandlung der Tiere mit Iproniazid wird im Herzen ebenfalls eine Anhäufung der beiden Hormone gefunden.

Es wird auch eine relativ grössere Inaktivierung des Adrenalins im Vergleich zu Noradrenalin festgestellt.

[5] M. GOLDSTEIN *et al.*, Fed. Proc. *19*, 295 (1960).
[6] G. COHEN *et al.*, J. clin. Invest. *38*, 1935 (1959).
[7] M. GOLDSTEIN *et al.*, to be published.
[8] M. SHOSHKES *et al.*, Circulation *20*, 17 (1959).