volumes of the incubation mixtures. The results of an experiment, referring to different L-lysine concentration used, are shown in Table II.

Table II. Uptake of L-lysine from the rat small intestine tissue. Fresh intestinal tissue: g 1; Substrate: L-lysine as shown in the 1st line, in Ringer-bicarbonate buffer, pH 7; 10 ml; Gas: 95% O_2 + 5% CO_2; duration of an experiment: 60 min; temperature: 38°C.

	μM L-lysine				
Before uptake	90	135	450	810	900
After uptake (60th min)	86	125	337	791	873
Uptake, i.e. theoretical amounts of L-lysine assumed during the experiment	4	10	13	19	27
L-lysine found in intestinal tissue slices after 10% TCA precipitation	2	9·5	11·5	17·5	25

3. L-lysine absorption tests in intact animals. The rats were anesthetised with ether, and the abdomen opened in its midline. The small intestine was then tied off at about 5 cm from the stomach, and in a similar manner at a lower level close to the ileo-cecal valve, with a silk thread. Just near both ligatures a little stoma on the intestinal wall was made, in order to place two small glass funnels at each open end of the intestine. A solution containing RINGER-bicarbonate buffer plus L-lysine was then delivered at the upper end of the intestine. Samples of lysine solution for analysis were taken from the lower glass funnel at fixed times. The results of three experiments are given in Table III.

Table III. Absorption of L-lysine from the rat small intestine *in vivo* L-lysine: 520 μM, in Ringer-bicarbonate buffer pH 7, 5 ml; duration of an experiment: 60 min.

Experiments	1	2	3
	μM L-lysine/h		
L-lysine found in the intestinal lumen after the experiment	73	82	86
Theoretical amounts of absorbed L-lysine	447	438	434

Conclusions. Experiments carried out on the rat small intestine, using different methods, show that L-lysine is taken up actively by the epithelial cells of the mucosa.

The uptake and absorption rates depend on the L-lysine present at various concentrations in the experimental systems.

A relationship has also been found between L-lysine concentration in the intestinal lumen and the rate of its appearance in the outer solution, i. e. the diamino acid transport through the intestinal wall. It is apparent, therefore, that an important limiting factor of the transport reactions in intestinal villi is the lysine concentration.

Acknowledgement: I am grateful to the Richter Co., Milan, and particularly to Dr. K. KORENIJ, for his kindness in supplying animals for the experiments.

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Zusammenfassung

L-Lysin wird durch die Rattendarmschleimhaut mit einer je nach den Anfangskonzentrationen verschiedenen Geschwindigkeit absorbiert. Die anfänglichen Lysinkonzentrationen stellen beim Transport der Diaminosäure durch die Darmvilli ein die Reaktionen abschwächendes Moment dar.

The Antagonism of Adrenergic Blockade by Dichloroisoproterenol (DCI)[1]

The compound dichloroisoproterenol (DCI)[2] has been described as a blocking agent of inhibitory adrenergic receptors[3] as well as of the inotropic and chronotropic receptors of the heart[4]. These results suggest that this drug is a specific antagonist of the hypothetical beta receptors (as described by AHLQUIST[5]) without exerting appreciable effects on the excitatory (alpha) adrenergic receptors. Thus, the vasodepressor and cardiac stimulant actions of isoproterenol or epinephrine are effectively antagonized by DCI, but no effect is seen against the pressor activity of epinephrine or norepinephrine.

In this report we wish to describe the effect of DCI in antagonizing the blockade of the epinephrine and norepinephrine pressor responses by several of the adrenergic blocking agents. All of these experiments were carried out in pentobarbital anesthetized dogs, and blood pressures were measured from the carotid artery with a mercury manometer. As can be seen in the Figure, the pressor responses to epinephrine and norepinephrine are reversed by a 10 mg/kg dose of dibenzyline. The vasodepressor effect of isoproterenol is not altered by the adrenergic blocking agent. When administered after dibenzyline DCI in doses of 5 to 15 mg/kg was found to produce a depressor response. Subsequent injections of epinephrine and norepinephrine no longer exhibited depressor responses, but were reconverted to pressor effects, indicating that the blockade of excitatory receptors by dibenzyline had been removed. This effect was seen whether the DCI was given 1, 3, or 5 h after the dibenzyline. In all instances the depressor response of isoproterenol was reduced or abolished after the DCI treatment. The magnitude of the epinephrine and norepinephrine pressor responses after the dibenzyline-DCI pretreatment varied with the different experiments, but in general they were at least 50 to 75% of control, and occasionally equal to control responses. If further doses of the adrenergic blocking agent were administered the reconverted pressor effects again decreased, but depressor responses to the catecholamines did not reappear. Similar results were obtained when dihydroergotamine or benzodioxane were employed as the adrenergic blocking agent.

These findings indicate that DCI alters not only the inhibitory (beta) adrenergic responses but also the excitatory effects of epinephrine and norepinephrine after adrenergic blockade. This is especially interesting with dibenzyline since blockade produced by drugs of this series is generally considered to be of the nonequilibrium type[6] with extremely prolonged durations of action[7,8]; yet the administration of DCI immediately restores the vasopressor actions of epinephrine and norepinephrine. The true nature of the observed antagonism of adrenergic

[1] This study was supported in part by a Research Training Grant from the National Institutes of Health.

[2] Dichloroisoproterenol is 1-(3,4-dichlorophenyl)-2-isopropylaminoethanol hydrochloride (Lilly 20522) and was generously supplied by Dr. I. H. SLATER of the Lilly Research Laboratories.

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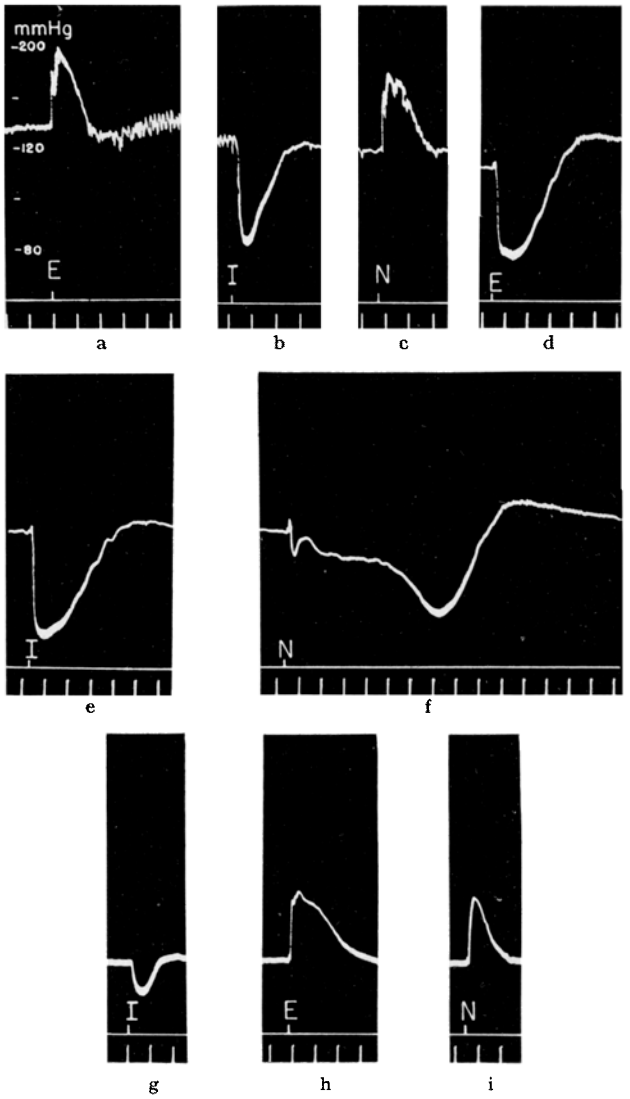

Recording of the carotid arterial blood pressure of a 8·4 kg male dog anesthetized with 30 mg/kg sodium pentobarbital (Nembutal) intravenously. E. l-epinephrine bitartrate, 5 μg/kg. I. l-isoproterenol hydrochloride, 5 μg/kg. N. l-arterenol bitartrate hydrate, 5 μg/kg. Between C and D the animal received 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.

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