m-tyramine, the longer lasting depletion cannot be explained on a displacement basis. A prolonged effect on the norepinephrine-binding sites or a slow rate of norepinephrine turnover in the tissues are more likely explanations. When α-methyl-*m*-tyrosine was administered in doses producing a maximal depletion of norepinephrine, barely detectable amounts of α-methyl-*m*-tyramine were found in the tissues.

Another conclusion from these studies is that α-methyl-*m*-tyramine is a more potent releaser of norepinephrine than is apparent when considerations are pased on the administered dose. The highest levels found in brain and heart, following dosages of α-methyl-*m*-tyramine which produced maximal norepinephrine-depletion (50 mg/kg), were about 1 and 8 μg/g, respectively. Based on the amounts of the drug actually reaching the tissues, α-methyl-*m*-tyramine and probably α-methyl-*m*-tyrosine and α-methyl-dopa may be as potent releasers of norepinephrine as are the Rauwolfia alkaloids. More detailed studies are now in progress.

Laboratory of Clinical Biochemistry,
National Heart Institute,
Bethesda, Md. U.S.A.

SIDNEY UDENFRIEND
R. CONNAMACHER
S. M. HESS*

* Present address: Squibb Institute for Medical Research, New Brunswick, New Jersey.

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Increased intestinal absorption of foreign organic compounds in the presence of ethylenediaminetetraacetic acid (EDTA)

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FOREIGN organic compounds of low lipid-solubility are poorly absorbed from the intestine mainly because of their inability to penetrate readily the lipid-like membrane of the intestinal epithelial cells.[1] It is also recognized that most organic compounds used as drugs have too large a molecular size to pass freely through the aqueous "pores" of the epithelial cell membrane or through the spaces which might exist between the cells.[2] Recently, Windsor and Cronheim[3] have reported that two lipid-insoluble acids, heparin and sulfopolyglucin, which are normally very poorly absorbed from the gastrointestinal tract, are absorbed to an appreciable extent when administered together with the chelating agent, sodium EDTA. The present investigation of the effect of EDTA on the intestinal absorption of several lipid-insoluble compounds shows that the chelating agent increases the extent of absorption of neutral and basic compounds, as well as that of acidic compounds, and suggests a possible mechanism for this action.

Male Sprague-Dawley rats (200–250 g), fasted for 18 hr but allowed free access to water, were anesthetized with pentobarbital and ether, and the small intestine was exposed through an abdominal incision. Ligatures were placed at the pylorus and the ileo-cecal junction, and the bile duct was ligated. In most of the experiments, the renal pedicles were ligated so that the blood level of poorly absorbed drugs would be high enough to measure. Five ml of an isotonic salt solution, pH 7·4 (NaCl in 0·03 M phosphate buffer), containing either 1–5 mmoles of a drug per liter, or the drug together with 10 mg of disodium EDTA per ml, was introduced into the intestine through the pyloric ligature, and the abdominal incision closed. After 1 hr, the intestine and its contents were removed from the animal, blood was obtained by cardiac puncture, and the samples were assayed for the drug. The extent of absorption was calculated from the difference between the amount of drug placed in the intestine and that recovered from the intestinal tissue and contents after 1 hr. Sulfanilic acid was estimated by the colorimetric method of Bratton and Marshall,[4] and ^{14}C-labeled substances from the radioactivity of 1 N NaOH solutions of the samples. Each drug was studied in 8–12 animals.

The extent of absorption of two neutral molecules, mannitol-1:6-^{14}C and inulin-^{14}C, was markedly increased in the presence of EDTA. For example, when administered alone, these compounds were absorbed scarcely at all (less than 2 per cent), but, when administered with the chelating agent, the degree of absorption rose to values ranging from 7 to 11 per cent. The enhancement of absorption was also apparent from the plasma levels of radioactivity, which were increased 5- to 6-fold in animals that had received EDTA.

The absorption of a quaternary ammonium compound, decamethonium-N-methyl-^{14}C, was similarly increased in the presence of EDTA. Thus, control animals absorbed 2–3 per cent of the administered drug, whereas animals that had received the chelator absorbed 11–15 per cent. Moreover, EDTA-treated animals had plasma levels of the drug 5–6 times higher than those of control animals.

Two organic acids, sulfanilic acid and EDTA-2-^{14}C, also showed an increase in absorption in the presence of EDTA. For example, both acids were absorbed to the extent of 11–14 per cent in control animals (concentration of labeled plus non-labeled EDTA was 1 mg/ml), but the degree of absorption rose to values of 26–32 per cent in the presence of 10 mg of EDTA per ml, and the plasma levels of the drugs were increased about 5-fold.

It is conceivable that EDTA might alter the rate of absorption of certain acidic drugs by interfering with their chelation of calcium ion or other metal ions in the intestinal lumen. On the other hand, since EDTA increases the absorption of some neutral and basic compounds that would not be expected to combine with calcium, a less specific mode of action is indicated; for example, the chelating agent might alter the permeability of the intestinal epithelium. To investigate the latter possibility, we have measured the extent to which inulin passes from the bloodstream into the intestinal lumen when the lumen contains either saline solution alone, or the same solution with 10 mg of EDTA per ml. The amount of intravenously administered inulin appearing in the lumen within 1 hr was increased 4-fold in the EDTA-treated animals, indicating that the permeability of the blood-intestinal boundary had been increased. Perhaps the chelating agent acts by increasing the size of the membrane "pores" or by widening the spaces between the epithelial cells through the removal of calcium ions.

Further work is in progress to clarify the mechanism by which EDTA increases the absorption of lipid-insoluble compounds.

Laboratory of Chemical Pharmacology,
National Heart Institute,
National Institutes of Health,
Bethesda, Md., USA.

LEWIS S. SCHANKER
JEAN M. JOHNSON

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