Thus it is unlikely that amantadine acts by inhibiting dopa decarboxylase in the peripheral sympathetic system.

Animals receiving amantadine and L-dopa, 250 mg/kg, were less jerky than those given L-dopa 700 mg/kg and showed a general appearance similar to that seen after treatment with apomorphine and clonidine by Andén, Corrodi & others, (1970).

Some of the animals receiving L-dopa, 350 mg/kg, after amantadine died in convulsions within 2 h. Similar convulsions, although less pronounced, were also seen in a few mice given L-dopa alone at 1000 mg/kg. This probably explains the reduction in motor activity found in the animals at these doses.

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Department of Pharmacology,
University of Göteborg,
Göteborg, Sweden.

T. H. SVENSSON
U. STRÖMBERG

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Intestinal blood flow and absorption of non-dissociable substances

Experiments concerning the influence of intestinal blood flow on absorption of drugs are rare. Ochsenfahrt & Winne (1969) have shown that the appearance of aniline, amidopyrine, antipyrine, benzoic and salicylic acid in the intestinal venous blood of rats is dependent on blood flow. These findings are now complemented by data of the following non-dissociable substances: tritiated water, methanol, ethanol, urea, ethylene glycol, glycerol, erythritol, and ribitol. Jejunal loops (6–10 cm) of urethane-anaesthetized and heparinized rats were perfused by an isotonic phosphate buffer (pH 7), or by Ringer solution containing the substances. The jejunal vein of the loop was punctured and the outflowing blood collected and weighed (= blood flow). The lost blood was substituted by an infusion of heparinized rat blood into the jugular vein. The intestinal blood flow was changed from high to low and from low to high values by varying the blood infusion. A drop recorder in the venous outflow provided a control record. The concentrations of the [^{14}C]-labelled substances and of tritiated water were measured in the collected blood. Appearance rate and blood flow are referred to wet tissue weight (Ochsenfahrt & Winne, 1969).

The results are summarized in Fig. 1. The figures are corrected to a concentration of 50 nmol/ml in the perfusion solution. Tritiated water showed the highest appearance rate which was almost strictly dependent on blood flow. The absorption rate and its dependence on blood flow decreased in the order ethanol, methanol, glycerol, ethylene glycol, urea, erythritol, and ribitol. The absorption of ribitol is independent of blood flow.

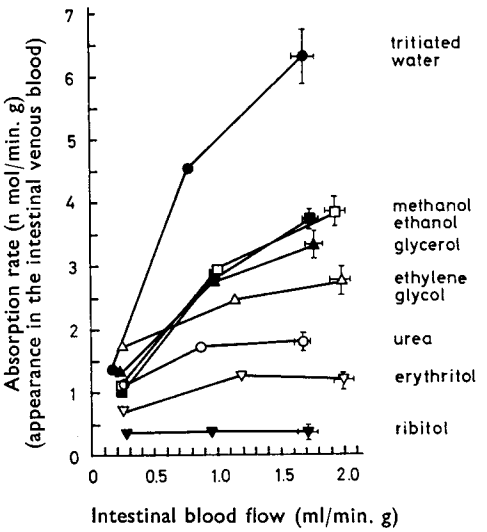

FIG. 1. Dependence of intestinal absorption on blood flow. Luminal perfusion of jejunal loops of rats. Data corrected to a concentration of 50 nmol/ml in the perfusion solution. 95% confidence limits.

For the theoretical interpretation of the curves a simplified equation can be derived from a three-compartment-model (Winne & Ochsenfahrt, 1967):

$$\phi = \frac{C_{DO} - C_{PA}}{\frac{1}{k\ F_D} + \frac{1}{\alpha a_1 V_B}}$$

ϕ = appearance rate in the intestinal venous blood (mol/min), C_{DO} = concentration in the luminal perfusion solution (mol/ml), C_{PA} = arterial plasma concentration (mol/ml), k = permeability coefficient of the epithelium (ml min^{-1} cm^{-2}), F_D = mucosal surface area (cm^2), α = fraction of blood flowing through capillaries near the epithelium, V_B = whole intestinal blood flow (ml/min), a_1 = concentration ratio blood to plasma. The denominator can be interpreted as resistance of the region between the intestinal lumen and the blood. The whole resistance is divided into two parts (first and second term of the denominator): (1) resistance of the region between the intestinal lumen and the capillary wall (mainly the resistance of the epithelium), (2) resistance of the drainage system. A high permeability of the epithelium means a small first term of the denominator, the second term with the blood flow determines the absorption rate. The appearance in the intestinal venous blood is blood flow-limited (example: tritiated water). A low permeability of the epithelium means a large first term of the denominator, the second one can be neglected. The absorption rate is independent of blood flow (example: ribitol).

Institute of Pharmacology,
University of Tübingen,
Germany.

D. WINNE
J. REMISCHOVSKY

April 22, 1970

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