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A note on the absorption of 3-methoxy-*N*-methylmorphinan hydrochloride from the rat stomach

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(+)-3-Methoxy-*N*-methylmorphinan, a base with a pK_a of 7·97 is absorbed from the rat stomach at pH 2·0, in a manner which suggests passive diffusion rather than a specialized transport process to be the mechanism.

IT is widely believed as a result of the "pH partition hypothesis" (Brodie, 1964) that amines, other than quaternary ammonium derivatives, can be absorbed only from the small intestine where the pH is such that a significant fraction of the drug is in the non-ionized and lipid-soluble form. However, drugs of the morphinan class form salts which have considerable lipid solubility, a factor which is used in their chemical assay (Divatia & Biles, 1961; Hull & Biles, 1964). *In vitro* transfer into an organic phase and the disappearance of (+)-3-methoxy-*N*-methylmorphinan hydrochloride from a solution held in the rat stomach *in situ* have now been examined. Although the salt forms ion pairs of limited lipid solubility (Higuchi, Michaelis & others, 1967), it does contain the only anion of consequence in the stomach.

Experimental

MATERIALS

The (+)-3-Methoxy-*N*-methylmorphinan was an analytical sample of dextromethorphan base (Vick). Sodium chloride, potassium chloride, calcium chloride, hydrochloric acid, sodium borate, monosodium dihydrogen phosphate, amyl alcohol, and chloroform were reagent grade. Cyclohexane was spectroscopically pure. Tropaeolin 00 dye (sodium *p*-diphenylamineazobenzenesulphonate, Eastman) was recrystallized four times from water. Normal heptane (Phillips Petroleum, Oklahoma) was redistilled and the fraction collected at 93°.

PHOSPHOLIPID EXTRACTION

The yolks of 12 eggs were washed with 400 ml of acetone and the residue extracted with 1500 ml of a 5% solution of ether in ethanol. The extract was evaporated to dryness in a rotary evaporator and the residue dissolved in 400 ml of ether and precipitated with 4 volumes of acetone. This precipitation procedure was repeated three times, giving a final yield of approximately 12 g of phospholipid extract having an approximate composition of 4 choline containing lipids to 1 ethanolamine containing lipid (Lea, Rhodes, & Stoll, 1955). It was used without further purification.

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DISTRIBUTION EXPERIMENTS

The dextromethorphan was transferred from a 0·1 M chloride buffer of pH 2 through an organic layer into a 0·1 M phosphate buffer, pH 7·4, using a cell and techniques as previously described by Perrin (1967). Preliminary experiments showed that a 25% solution of cyclohexane in amyl alcohol (v/v) gave a suitable transfer rate, and various known quantities of phospholipid were dissolved in this solvent and also used as the lipid phase. In none of the experiments was any significant amount of drug found to have passed through the organic phase into the pH 7·4 phase. The experiments were made at 25° ± 0·5°. The two aqueous phases were assayed in a manner similar to that later described. The organic layer was not assayed.

In vivo EXPERIMENTS

Sprague-Dawley female rats weighing approximately 150 g were fasted for 24 hr in cages with wide mesh floors to reduce coprophagy, with water freely available. After weighing, the animals were anaesthetized with urethane (approximately 150 mg 100 g body weight). The stomach was exposed and ligated immediately adjacent to the cardiac sphincter, care being taken not to tie off any major blood vessels. A second ligature

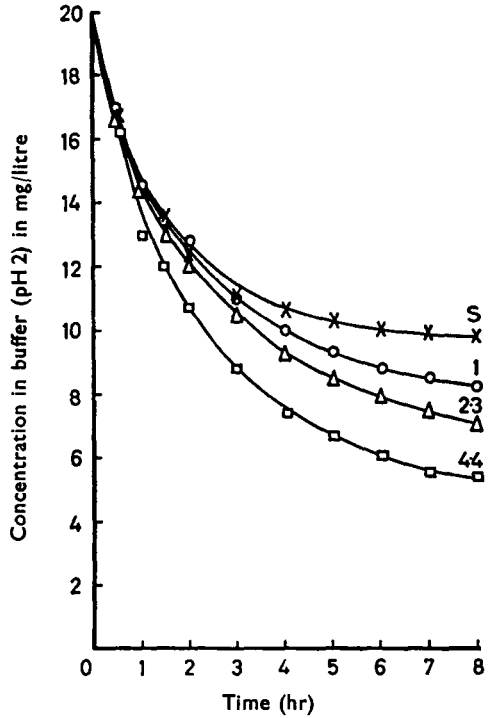

FIG. 1. Effect of phospholipid on the transfer of (+)-3-methoxy-*N*-methylmorphinan hydrochloride from pH 2·0 buffer into an organic phase of 75% amyl alcohol in cyclohexane. Solvent(S) and phospholipid concentrations are given on the curves.

was placed adjacent to the pyloric sphincter. A needle was introduced through the duodenum to project into the stomach via the pyloric sphincter before the ligature was finally secured after which, the drug was injected as a 3 ml dose in a pH 2·0 chloride buffer made isotonic (similar to Ringer solution) to prevent water absorption. The needle was then removed and the incision closed. After the desired time interval, the incision was opened, the stomach removed, and the animal killed. The contents of the stomach were removed with successive washings of normal saline to make a final volume of 25 ml after filtration through glass wool. Animals with food in their stomachs were rejected.

EXTRACTION AND ASSAY

To the saline washings was added 10 ml 0·1 M borate buffer pH 10 to give pH 9·5 approximately, and this aqueous phase was extracted with two 50 ml portions of normal heptane. The heptane was then extracted with 20 ml of a 0·1 M phosphate buffer pH 2·8. To 2 ml of this solution were added 2 ml of a pH 3·4, 0·1 M phosphate buffer, and 2 ml of a 4×10^{-4} tropaeolin 00 dye solution in water. The drug-tropaeolin

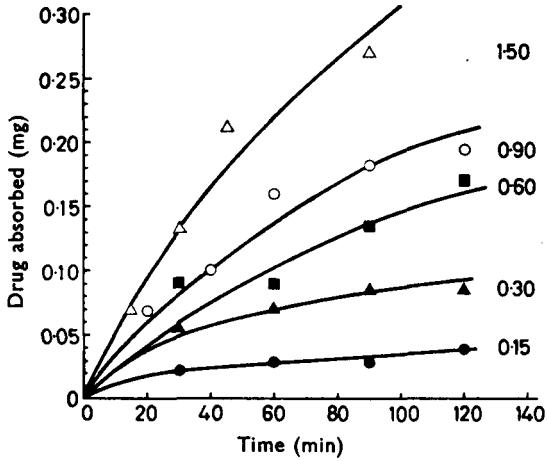

FIG. 2. Absorption of (+)-3-methoxy-*N*-methylmorphinan hydrochloride from rat stomach at pH 2. Figures on curves are doses in mg.

ion-pair was then extracted into 5 ml of chloroform, and the extinction measured at 410 mμ in a Cary 11 spectrophotometer. The washed stomachs were homogenized and extracted in a manner similar to that described and were found to contain little or no drug. Blank experiments in which 3 ml isotonic buffer containing no drug were given to the animals gave zero extinction when assayed in the above manner.

Results and conclusions

The effect of phospholipid on the rate of transfer of the drug from the pH 2·0 phase to the organic phase is shown in Fig. 1. The phospholipid

increases the rate and extent of transfer, but did not transfer the drug to the pH 7·4 phase. The drug clearly has an affinity for the phospholipid, a fact which we also observed in preliminary optical rotary dispersion investigations. We have also observed that the drug can penetrate a lecithin monolayer at a pH 2·0.

The *in vivo* investigations can be summarized by Fig. 2. Dextromethorphan has a pK_a of 7·97 which means that at pH 2 approximately one molecule in 10^6 is in the unionized state, suggesting that the drug transfer must involve the positively charged species. From Fig. 2 it can be seen that the extent of uptake increases in an almost regular manner with the dose level and does not become saturated. This suggests that absorption of this tertiary amine is by passive diffusion and not by the specialized transport process thought to be responsible for the transfer of quaternary amines. Shanker, Shore & others (1957), discussing the absorption of organic bases from the rat stomach and advancing the pH partition hypothesis, noted in preliminary experiments, that some absorption of dextromethorphan took place from a 0·1 M hydrochloric acid solution in the rat stomach, but they were unable to confirm this. The role of the anion in the absorption reported here is not clear and this is being investigated.

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