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Destruction of chlorpromazine during absorption by rat intestine *in vitro*

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It is commonly supposed that orally administered chlorpromazine is rapidly and well absorbed in man, although there appears to have been no systematic investigation of the absorption phenomenon (Goodman & Gilman, 1965; Shepherd, Lader & Rodnight, 1968). Doubt was recently cast on the supposition by measurements of unchanged chlorpromazine in plasma of man and animals (Curry, Davis, Janowsky & Marshall, 1970; Hollister, Curry, Derr & Kanter, 1970; Curry, Derr, Maling & Williams, 1970); concentrations of unchanged drug in plasma after injected doses were 3–10 times higher than those after oral doses during the 48 h following administration. This indicated *incomplete* absorption of oral doses as unchanged drug. In contrast, concentrations of metabolites of chlorpromazine in urine after doses by the two routes were similar. This indicated *complete* absorption, either as unchanged drug as or metabolites. We therefore investigated the possibility that the drug could be converted to absorbable metabolites during the process of absorption.

Krebs bicarbonate fluid containing ^{35}S-chlorpromazine (50, 100 and 200 μg/ml) was circulated at 37° C through the lumen of rat isolated intestine. The serosal surface was bathed with a similar solution containing no chlorpromazine (technique of Fisher & Parsons, 1949). Unchanged chlorpromazine, measured by gas chromatography, disappeared rapidly from the luminal solution and was partially transferred to the serosal solution and partially retained in the intestinal wall. Concentrations of total radioactivity and of unchanged chlorpromazine were similar both in the luminal solution and in the intestinal wall. In contrast, radioactivity appeared in the serosal solution more rapidly than did unchanged chlorpromazine; at the end of the experiment (60 min), 15–32% of the serosal radioactivity was present as unchanged drug.

These observations indicated that chlorpromazine was decomposed during absorption *in vitro*. The mechanism of this decomposition is not clear, but results of control experiments demonstrated that chemical decomposition unrelated to the presence of intestinal material did not occur. Biochemical decomposition may have been brought about by intestinal flora or enzymes in the intestinal wall. If this process were to occur *in vivo* it might be the cause of concentrations of unchanged drug in plasma being less after oral doses than after injected doses.

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Reflex and other vascular changes in anaesthetized dogs after β-adrenoceptor antagonism with alprenolol, bunolol and propranolol

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The purpose of this investigation was to compare reflex and other vascular changes produced by alprenolol with those of other β-adrenoceptor blocking agents which are devoid of stimulant activity on β-adrenoceptors. Intravenous doses of propranolol (0·5 mg/kg), alprenolol (0·5 mg/kg) (Åblad, Brogård & Ek, 1967) and bunolol (0·2 mg/kg) (Robson, Simon & Thompson, 1970; Kaplan & LaSala, 1970) were selected to cause equal β-adrenoceptor antagonism, as shown by the inhibition of the increase in heart rate produced by isoprenaline.

Dogs of either sex were anaesthetized with a mixture of barbitone sodium (300 mg/kg intravenously) and pentobarbitone sodium (approximately 20 mg/kg intravenously). Dogs used in femoral perfusion studies were anaesthetized with chloralose (100 mg/kg intravenously). A Sigmamotor pump was used to autoperfuse a hind limb through the femoral artery. The spleen was enclosed in a Perspex container and pressure changes in the enclosed system recorded as indicative of changes in spleen volume. Aortic flow was detected by a probe placed round the ascending aorta and measured with an electromagnetic flowmeter. Heart rate was recorded by a cardiotachometer triggered by the electrocardiogram. Systemic arterial blood and other pressures were measured with appropriate transducers and recorded on a Beckman Type R dynograph.

The selected doses of the blocking agents administered to groups of three or four dogs caused bradycardia and significant ($P<0·01$) reductions in spleen volume. Blood pressure was most depressed by alprenolol. Subsequent doses of bunolol or propranolol were ineffective, but the splenic and depressor effects persisted with later doses of alprenolol. The splenic contractions were prevented or abolished by splenic nerve section or ganglion blockade in normal or adrenalectomized dogs, and the response, therefore, appeared to be reflexly mediated. After these procedures, alprenolol still caused hypotension and frequently caused splenic relaxation. The relatively weak β-sympathomimetic *dextro*-isomer (Åblad *et al.*, 1967) had less depressor activity and induced smaller splenic changes than *racemic* alprenolol in each of three dogs. Thus, the β-sympathomimesis of alprenolol may be responsible for the above differences, their persistence after bunolol or propranolol indicating that the selected doses were insufficient to prevent the sympathomimesis of alprenolol (0·5 mg/kg).

In chloralose-anaesthetized animals, propranolol (six dogs) and bunolol (five dogs) increased femoral perfusion pressure ($P<0·01$), but alprenolol (seven dogs) had little effect. Only alprenolol caused a significant fall ($P<0·01$) in diastolic blood pressure.