Isoprenaline conjugation—a "true first-pass effect" in the dog intestine

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The term 'first-pass effect' was coined by Harris & Riegelman (1969) to describe the reduction in the bioavailability of aspirin seen after oral as compared to intravenous administration. They ascribed this observation to metabolism in both the intestine and the liver before drug reached the systemic circulation. It is now recognized that a wide variety of drugs shows a significant 'first-pass effect' (Routledge & Shand 1979) which results from uptake and/or metabolism in the intestine, liver or lung. Although the major part of such elimination occurs on the 'first-pass' through these organs many drugs continue to be similarly extracted in subsequent circulations. The term 'first-pass effect' is therefore somewhat misleading and Routledge & Shand (1979) have recently suggested that 'presystemic drug elimination' may be a more appropriate description.

Conolly et al in 1972 showed that after intravenous administration of isoprenaline to man and dog unchanged isoprenaline and its 3-*O*-methyl metabolite were the only compounds found in plasma and urine. In contrast, after oral administration of the drug, conjugates of isoprenaline were the major metabolites in plasma and urine. Later the site of conjugation was shown to be the intestinal wall and the conjugate identified as isoprenaline sulphate (George et al 1974). This work suggested that isoprenaline in the systemic circulation did not readily gain access to the sulphokinase enzymes in the gastrointestinal tract. Several similar route-dependent differences in metabolism have also been noted (Conway et al 1973; Evans et al 1973; Støa & Levitz 1968).

In the present study we have used an in situ preparation of dog jejunum to further investigate the metabolism of isoprenaline in the intestine. The anaesthetized dog preparation was essentially as previously described (George et al 1974) and [^{3}H]isoprenaline (The Radiochemical Centre, 15·4 Ci mmol^{-1}) was infused (305 ng/0·1 ml min^{-1} for 30 min) directly into the arterial supply leading to the in situ loop of jejunum. Venous blood from the loop was collected in 3 min fractions for 30 min and arterial blood samples were taken from the abdominal aorta at the same times. Total radioactivity was measured in aliquots of both arterial and venous plasma and these results are shown in Fig. 1. Levels of radioactivity in venous plasma were some two orders of magnitude greater than those in the arterial plasma indicating little spill-over of drug into the systemic circulation. Unchanged isoprenaline in venous plasma was measured by the method of Conolly et al (1972) and corrected for recovery which was 81·2 ± 0·7% (mean ± s.e.m., n = 8). Total radioactivity in venous blood from the jejunal loop was all accounted for as unchanged isoprenaline (102·8 ± 1·3%; mean ± s.e.m., n = 10). The net rate of uptake of isoprenaline by the loop (Fig. 1) was calculated from a knowledge of the infusion rate into the arterial blood and the amount recovered in venous plasma using a red blood cell/plasma partition coefficient of 0·98. During the 30 min infusion some 68·5% of infused [^{3}H]isoprenaline was taken up by the intestinal loop but no measurable amount of conjugated isoprenaline was found in the venous effluent. Hence it is concluded that intravenous isoprenaline does not penetrate readily to the intestinal sulphokinase enzymes and we suggest that orally administered isoprenaline is the first documented example of a drug showing 'true first-pass' metabolism in the intestine.

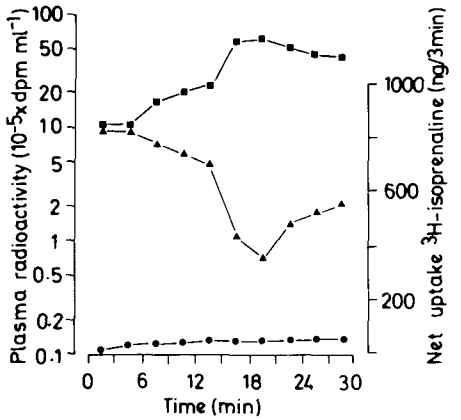

FIG. 1. Levels of radioactivity in venous plasma from the in situ loop of dog jejunum (■—■) and in aortic plasma (●—●) during a close intra-arterial infusion of [^{3}H] isoprenaline. Also shown is the net rate of uptake of [^{3}H] isoprenaline by the loop (▲—▲).

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