The effect of a new β_2-adrenoceptor agonist, salmefamol, on pentagastrin-induced gastric acid secretion in conscious dogs

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Adrenoceptor agonists are known to decrease mammalian gastric acid secretion (Harries, 1956). The β-adrenoceptor agonist isoprenaline is more effective than the α-adrenoceptor agonist noradrenaline as an inhibitor of gastric acid secretion and the inhibition by isoprenaline is not secondary to a decrease in mucosal blood flow (Curwain & Holton, 1972). Investigations have shown that the β_2-selective adrenoceptor agonist salbutamol also inhibits gastric secretion (Curwain, Fielding & Russell, 1974; McCloy, Dawson & Baron, 1976) although the mechanisms remain uncertain.

In the present study a new, potent β_2-selective adrenoceptor agonist, salmefamol (Figure 1) was tested for its effect on pentagastrin-induced gastric acid secretion in conscious dogs.

Five dogs (2 female, 3 male, 26–31 kg) each with a well established gastric fistula, were used. In the first set of experiments maximal acid secretion was produced by continuous i.v. infusion of pentagastrin (8 μg kg^{-1} h^{-1}). Salmefamol was infused concurrently for 60 min at one of five dose levels ranging logarithmically from 0.05 to 0.8 μg kg^{-1} min^{-1}. The output of acid in the last 30 min of the salmefamol infusion was compared with the equivalent period in a control experiment, where pentagastrin alone was infused, and the percentage inhibition calculated. The pulse rate was measured by palpation.

The second set of experiments determined the effects of β-adrenoceptor antagonists on the response to salmefamol by administering practolol (0.2 and 0.5 mg/kg) or propranolol (0.1 mg/kg) 15 and 30 min before commencing the salmefamol infusion (0.2 μg kg^{-1} min^{-1}).

In the final set of experiments the dose of salmefamol producing 50% inhibition of acid secretion (0.1 μg kg^{-1} min^{-1}) was tested against six logarithmically increasing pentagastrin doses ranging from 0.25 – 8 μg kg^{-1} h^{-1}. The inhibition of secretion by each dose of salmefamol being calculated by reference to a control experiment with pentagastrin, statistical differences were determined by Student's *t* test for paired observations.

The acid output was significantly reduced ($P < 0.05$) in a dose related manner by salmefamol 0.1 to 0.8 μg kg^{-1} min^{-1}. The highest dose inhibited secretion by 89 ± 4% (mean ± s.e. mean) with an increase of 96 ± 22% in pulse rate. The acidity of the gastric juice was also reduced. Propranolol abolished the inhibition of acid secretion and tachycardia induced by salmefamol whereas practolol had no effect on the antisecretory response but did reduce the tachycardia.

Salmefamol significantly depressed the response to all doses of pentagastrin ($P < 0.05$) and linear transformation of these curves showed a change in the slopes.

Calculation of Michaelis-Menten constants using the Eadie-Hofstee transformation of response versus response/dose (Dowd & Riggs, 1965) showed a significant decrease in calculated maximal response ($P < 0.05$) and an unchanged $D_{(50)}$ which indicates a non-competitive inhibition.

Thus it has been shown that salmefamol inhibits pentagastrin induced gastric acid secretion in the conscious dog. Kinetic studies indicate that the inhibition is by a non-competitive mechanism. This inhibition is probably mediated via β_2-adrenoceptors since the antisecretory effects were blocked by propranolol but not practolol.

References

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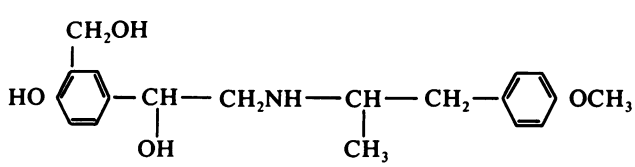

Figure 1 Structure of Salmefamol.