THE EFFECT OF 
(−)-ISOPRENALELINE AND (±)-SALBUTAMOL 
ON PEPSONGEN AND ACID SECRETION IN THE DOG

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1 The β-adrenoceptor agonists, (−)-isoprenaline and (±)-salbutamol, reduced pepsinogen secretion 
induced by pentagastrin in conscious dogs with Heidenhain pouches.
2 (−)-Isoprenaline and (±)-salbutamol also reduced gastric acid secretion while producing a moderate tachycardia.

Introduction

β-Adrenoceptor agonists inhibit gastric acid secretion 
induced by pentagastrin and food in the dog (Curwain 
& Holton, 1972) and man (Fielding, Kilborn & 
Russell, 1975). However, little is known about the 
effects of β-adrenoceptor agonists on pepsinogen 
secretion. Holton (1973), reviewing the available 
information, concluded that catecholamines probably 
stimulate pepsinogen secretion. We wish to report 
studies in which the β-adrenoceptor agonists (−)- 
isoprenaline and (±)-salbutamol inhibited pepsinogen 
secretion induced by pentagastrin in conscious dogs 
with vagally denervated (Heidenhain) pouches.

Methods

Male beagle dogs (13.3–15 kg) with well-established 
Heidenhain pouches were used. Food was withheld 
but water allowed for 18 h before each experiment. 
The dogs stood in slings during the experiment. A 
sterile catheter was inserted into a superficial limb vein 
and an infusion of sterile saline (0.9% w/v NaCl 
solution) given at the rate of 1 ml/minute. All drugs 
were administered in this saline infusion.

Submaximal gastric secretion was induced by a 
continuous infusion of pentagastrin. In each dog a 
dose of pentagastrin which would give a 50% maximal 
secretory response was determined as follows. 
Pentagastrin was infused at 0.5 μg kg⁻¹ h⁻¹ for 1 h or 
until a plateau of gastric acid secretion was obtained. 
The dose of pentagastrin was then doubled, and this 
dose infused until a new plateau of secretion was 
reached. The procedure was repeated until doubling 
the dose of pentagastrin produced no further increase 
in gastric acid secretion. Secretory responses were 
calculated as percentage of maximum response to 
pentagastrin and the dose required to elicit 50% of 
maximum secretion was determined for each dog. 
These pentagastrin doses, which were used for all 
further experiments, were 1, 4 and 4 μg kg⁻¹ h⁻¹ for 
dogs 1, 2 and 3 respectively.

The pouch secretion was allowed to drain into a 
collection vessel which was changed every 15 minutes. 
The volume of secretion was measured to the nearest 
0.1 ml and an aliquot titrated against 0.1 mol/l NaOH 
to pH 7 using a Radiometer TTT2 titration system. 
Acid output was calculated in μmol H⁺/minute. The 
remaining sample was deep frozen for subsequent 
determination of pepsin content by a modification of 
the autoanalyser method of Vatier, Cheret & Bonfils 
(1968). Pepsin content is expressed in pepsin units 
where 1 pepsin unit is the enzymatic activity required 
to release 1 μmol of tyrosine per min from 4% ox 
haemoglobin substrate at pH 2.0 and 37°C. Heart 
rate was measured at 15 min intervals by palpation.

Once a plateau of gastric acid secretion had been 
obtained (less than 10% variation over 1 h), (−)- 
isoprenaline 1 or 3 ng kg⁻¹ min⁻¹ or (±)-salbutamol 
30 or 100 ng kg⁻¹ min⁻¹ was infused concurrently 
with the pentagastrin for 1 hour. Inhibition of 
secretion started in the first 15 min collection period 
and achieved equilibrium during the last 30 min of the 
infusion. Infusion of pentagastrin alone was then 
continued until the secretory response returned to the 
control level. Only one dose level of β-adrenoceptor 
agonist was administered in each experiment and at 
least 5 days elapsed between experiments.

Results have been calculated as % change in the 
measured parameters, by comparing the mean of the 
two consecutive values at peak drug response with the 
mean of the four control values preceding the drug 
infusion.

The drugs used were (−)-isoprenaline bitartrate 
dihydrate (Ward, Blenkinsop & Co. Ltd.), (±)-
Results

In each dog the control values for volume (secretion rate ml/min) and acid (secretion rate µmol H+min) secreted by the Heidenhain pouch submaximally stimulated by pentagastrin were consistent from experiment to experiment. The concentration of pepsin in units/l and in consequence the rate of pepsin secretion in units/min was more variable. Control heart rates were consistent for each dog. The mean control values ± standard error (n = number of experiments) for dog 1 were as follows: acid secreted 61.6 ± 3.0 µmol H+/min, volume secreted 0.42 ± 0.02 ml/min, pepsin concentration 86.6 ± 26.8 units/l, pepsin secretion rate 23.3 ± 7.4 units l × 10−3/min and heart rate 68.6 ± 2.7 beats/min (n = 11). For dog 2 corresponding values were, 43.8 ± 3.4, 0.30 ± 0.02, 136.4 ± 39.5, 45.7 ± 14.0 and 65.4 ± 3.1 (n = 9). For dog 3 corresponding values were, 14.7 ± 1.3, 0.12 ± 0.01, 123.9 ± 21.4, 13.7 ± 2.3 and 76.2 ± 2.7 (n = 11). The secretory outputs for each dog were approximately 50% of their maximum response to pentagastrin and the magnitude of the response probably reflects the pouch size.

The results summarized in Table 1 show that (−)-isoprenaline (1 and 3 ng kg−1 min−1) and (+)-salbutamol (30 and 100 ng kg−1 min−1) infusion over 1 h reduced the volume of gastric secretion, the rate of acid and pepsinogen secretion in a dose-related manner. The respective ED50 values in ng/kg (95% confidence limits) for (−)-isoprenaline were 2.1 (1.8–2.6), 2.3 (2.0–2.7) and 1.9 (1.5–2.7). The corresponding values for (+)-salbutamol were 56.1 (24–104), 62.0 (20–233) and 53.9 (19–164).

The concentration of pepsinogen was not significantly changed by (−)-isoprenaline or (+)-salbutamol and ED50 values were not calculated. The concentration of acid in the secretion did not alter significantly in response to (−)-isoprenaline or (+)-salbutamol administration.

(−)-Isoprenaline and (+)-salbutamol caused dose-related increases in heart rate, with a maximum increase of 76 and 107 beats/min respectively at the highest dose levels. All responses to (−)-isoprenaline showed complete recovery within 15–30 min and those to (+)-salbutamol within 45–180 min of the end of the drug infusion.

Discussion

In the present study using conscious dogs with Heidenhain pouches, intravenous infusion of total doses of 0.06 and 0.18 µg/kg (−)-isoprenaline or 1.8 and 6 µg/kg (+)-salbutamol inhibited pepsinogen secretion. These doses also produced tachycardia and are in the dose range eliciting β1-adrenoceptor mediated responses (Daly, Farmer & Levy, 1971; Daly, Flock & Levy, 1975). The potency of (+)-salbutamol relative to (−)-isoprenaline as an inhibitor of pepsinogen secretion was 28 compared with values of 6 to 25 for β2-adrenoceptor systems in the dog (Daly et al., 1971) suggesting that the observed inhibition of pepsinogen secretion is mediated through β2-adrenoceptors. Attempts to antagonize the effects of (−)-isoprenaline on gastric secretion with propranolol yielded equivocal results due to potentiation of pentagastrin-induced secretion by propranolol (Lin & Evans, 1973; Daly & Stables, unpublished results).

The inhibition of pentagastrin-induced gastric acid secretion by (−)-isoprenaline and (+)-salbutamol confirms other studies with (±)-isoprenaline (Curwain & Holton, 1972) and (+)-salbutamol (Curwain, Holton & Spencer, 1972). It has been proposed that β-adrenoceptor agonists reduce pentagastrin-stimulated

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose ng kg−1 min−1 for 60 min</th>
<th>Mean % change ± standard error</th>
<th>n</th>
</tr>
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<tr>
<td>(−)-Isoprenaline</td>
<td>1</td>
<td>Acid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−23.3 ± 4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−62.9 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>(±)-Salbutamol</td>
<td>30</td>
<td>−33.8 ± 8.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>−58.5 ± 8.8</td>
<td>7</td>
</tr>
</tbody>
</table>

* units as defined in methods
n = number of experiments.
acid secretion by inhibiting histamine formation or release (Curwain, Holton, McIsaac & Spencer, 1974; Lundell & Svensson, 1974). However, the site and mechanism of action by which (-)-isoprenaline and (+)-salbutamol inhibit pepsinogen secretion are unknown and their elucidation requires further investigation.

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References


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