Effect of a synthetic gastrin-like pentapeptide upon the intestinal transport of sodium, potassium, and water

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In addition to its marked stimulation of the stomach to secrete acid, the antral hormone, gastrin, can affect other functions of the alimentary tract. Thus, the highly active preparation of gastrin extracted from hog antral mucosa has been shown to stimulate the motility of the stomach and jejunum, to increase the tone of the gall bladder, and to augment the flow of pancreatic juice and hepatic bile (Gregory and Tracy, 1964).

The entire range of physiological activity displayed by natural gastrin is possessed by the C-terminal tetrapeptide-amide, tryptophan, methionine, aspartic acid, and phenylalanine NH₂ (Tracy and Gregory, 1964). The synthetic analogue, which has been produced by the Imperial Chemical Industries (I.C.I. 50,123) and has t-butyloxycarbonyl-β-alanine added to the functional tetrapeptide sequence, seems to have the properties of natural gastrin although it is probably less potent on a molar basis (Konturek and Grossman, 1966; Wormsley, Mahoney, and Ng, 1966; Logan and Connell, 1966). Because one of the important functions of gastrointestinal tracts is the absorption of water and electrolytes, we decided to study the effect of the gastrin-like pentapeptide upon the intestinal handling of sodium, potassium, and water.

METHODS

The experiments were performed in trained, placid mongrels, weighing 10-12 kg., in whom segments of jejunum (two dogs), ileum (two dogs), and colon (one dog) were isolated as Thiry-Vella fistulas. The serosal surface area of the intestinal segments measured approximately 100 cm². The details of the animal preparation and of the technique of measuring the rates of net transport and unidirectional fluxes of sodium, potassium, and water have been given elsewhere (Shields, Mulholland, and Elmslie, 1966).

Briefly, the isolated intestinal segments were first rinsed with modified Tyrode’s solution (Code and McIntire, 1956) at pH 7 and 37°C, until the returning fluid was clear. After 30 minutes, exactly 25 ml. test solution was instilled into the lumen of the fistula. At 10 minutes as much as possible of the luminal solution was withdrawn and the segment immediately irrigated with 100 ml. non-radioactive Tyrode’s solution. From the radioactivity acquired by this solution, the volume of test solution, which could not be aspirated at 10 minutes, was calculated.

The instillation of solutions into, and their withdrawal from, the isolated intestinal segments were facilitated by modified Foley catheters (Code, Bass, McClary, Newnum, and Orvis, 1960) which were inserted into each end of the fistula, leakage being prevented by inflation of the balloons of the catheters.

Two further 10-minute absorption tests were carried out in a similar manner at 1½ and 2½ hours after the end of the first test. The three absorption tests constituted a single experiment.

During all experiments an isotonic solution of sodium chloride was infused intravenously at a rate of 10 ml. per hour by a Palmer constant-rate infusion pump. In some experiments, the pentapeptide (I.C.I. 50,123) was added to the infusion solution to supply a dose of 4 μg. or 8 μg. per kilogram body weight per hour. In control experiments the saline solution was infused alone.

TEST SOLUTION

The test solution was modified Tyrode’s solution (Code and McIntire, 1956) containing the radioactive isotopes of sodium (4Na—2 μc./litre solution) and of potassium (4K—4 μc./litre solution), and the stable isotope of water, deuterium oxide (D₂O—1% v/v). The reaction of the solution, the temperature of which was maintained at 37°C, was brought to pH 7 with 0.1N hydrochloric acid.

ESTIMATIONS

The concentrations of sodium and potassium in the test solution were estimated by flame photometry. The separate activities of 4Na and 4K in mixtures were determined by differential counting in a well-type scintillation counter and in a Geiger-Müller M6 tube, with a wall 1 mm thick (Veall and Vetter, 1958). The concentration of D₂O was determined by infrared spectroscopy using a modification (Shields et al., 1966) of the method of Berglund-Larsson (1956).

1A preliminary report of this work was read to the Surgical Research Society (Gingell, Davies, and Shields, 1966), and it was carried out in laboratories which were built from funds given by the Wellcome Trustees.
CALCULATIONS The rates of movement of sodium, potassium, and water into and out of the intestinal lumen were determined from the formulae of Visscher, Fetcher, Carr, Gregor, Bushey, and Barker (1944a) and Visscher, Varco, Carr, Dean, and Erickson (1944b).

The errors of the method and the assumptions inherent in the calculations have been discussed in detail (Shields et al., 1966).

TERMINOLOGY Sodium, potassium, and water move simultaneously in both directions across the intestinal mucosa. 'Absorption' of a substance is applied to the situation where more of the substance leaves the intestinal lumen and enters the body than moves in the opposite direction into the intestinal lumen. 'Secretion' represents the converse situation, where the substance enters the intestinal lumen more rapidly than it leaves. The terminology describing the directions of movement of water and electrolytes across the intestinal mucosa has been reviewed (Shields, 1964).

RESULTS

NET TRANSPORT (TABLE I) In control experiments sodium and water were absorbed by the isolated segments of jejunum, ileum, and colon. The rates of net transport of these substances were greater in the ileum and colon than in the jejunum. Potassium was secreted by the small intestine but was absorbed by the colon.

When the synthetic gastrin-like pentapeptide was infused at rates of 4 and 8 μg. per kilogram per hour, the rates of absorption of sodium and water were significantly reduced in the ileum. The pentapeptide had no effect upon the net transport of these substances in the jejunum or in the colon.

In the jejunum the secretion of potassium was significantly increased when the pentapeptide was infused intravenously at rates of 4 and 8 μg. per kilogram per hour. In the ileum, the rate of potassium secretion was increased during the infusion of 4 μg. per kilogram per hour, but not with the larger dose of pentapeptide. The net transport rate of potassium in the colon was not affected by the intravenous infusion of the pentapeptide.

UNIDIRECTIONAL MOVEMENTS (TABLE I) When the pentapeptide was given at a rate of 4 μg. per kilogram

<table>
<thead>
<tr>
<th>Site</th>
<th>Experiment</th>
<th>Sodium Transport (μ-equiv./10 min.)</th>
<th>Potassium Transport (μ-equiv./10 min.)</th>
<th>Water Transport (ml./10 min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Net¹</td>
<td>Out of Lumen</td>
<td>Into Lumen</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Control (9)</td>
<td>+2.26</td>
<td>417±31</td>
<td>415±32</td>
</tr>
<tr>
<td></td>
<td>2 Pentapeptide-4 μg/kg/hr. (12)</td>
<td>-6.44</td>
<td>564±3</td>
<td>628±38</td>
</tr>
<tr>
<td></td>
<td>Difference between 1 and 2</td>
<td>Mean ± S.E.</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Jejunum</td>
<td>66±55</td>
<td>147±56</td>
<td>213±73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.2±</td>
<td>2±6</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2±</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>3 Pentapeptide-8 μg/kg/hr. (5)</td>
<td>+21±52</td>
<td>557±88</td>
<td>536±112</td>
</tr>
<tr>
<td></td>
<td>Difference between 1 and 3</td>
<td>Mean ± S.E.</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Jejunum</td>
<td>19±52</td>
<td>140±76</td>
<td>121±91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4±</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7±</td>
<td>&gt;0.05</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Ileum</td>
<td>Control (20)</td>
<td>+190±25</td>
<td>671±36</td>
<td>481±34</td>
</tr>
<tr>
<td></td>
<td>2 Pentapeptide-4 μg/kg/hr. (6)</td>
<td>+31±48</td>
<td>619±16</td>
<td>588±53</td>
</tr>
<tr>
<td></td>
<td>Difference between 1 and 2</td>
<td>Mean ± S.E.</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td>159±53</td>
<td>52±67</td>
<td>107±69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0±</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01±</td>
<td>&gt;0.4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td></td>
<td>3 Pentapeptide-8 μg/kg/hr. (3)</td>
<td>+11±17</td>
<td>377±135</td>
<td>366±119</td>
</tr>
<tr>
<td></td>
<td>Difference between 1 and 3</td>
<td>Mean ± S.E.</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td>179±67</td>
<td>294±105</td>
<td>115±98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.7±</td>
<td>2±8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.02±</td>
<td>&lt;0.02</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Colon</td>
<td>Control (3)</td>
<td>+11±58</td>
<td>389±97</td>
<td>231±211</td>
</tr>
<tr>
<td></td>
<td>2 Pentapeptide-4 μg/kg/hr. (3)</td>
<td>+120±80</td>
<td>381±180</td>
<td>261±105</td>
</tr>
<tr>
<td></td>
<td>Difference between 1 and 2</td>
<td>Mean ± S.E.</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>38±134</td>
<td>8±243</td>
<td>30±207</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3±</td>
<td>0.03</td>
<td>0±</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7±</td>
<td>&gt;0.9</td>
<td>&gt;0.8</td>
</tr>
</tbody>
</table>

¹ The plus and minus signs preceding the mean rates of net transport indicate absorption and secretion respectively.

² The figures in parenthesis indicate the number of experiments.
per hour, potassium entered the lumen of the jejunum, ileum, and colon more rapidly than in the control experiments. When the rate of infusion of pentapeptide was doubled, the increase in the rate of potassium movement into the lumen was maintained in the jejunum. Also, in the jejunum, at both rates of pentapeptide infusion, potassium moved more rapidly out of the lumen than in control experiments. In the ileum at the higher rate of infusion the rates of unidirectional movement of potassium did not differ significantly from those in control experiments.

The pentapeptide had no constant effect upon the unidirectional fluxes of sodium and water.

**CONCENTRATION OF ELECTROLYTES IN THE LUMINAL SOLUTION (TABLE II)** In control experiments the concentration of sodium in the jejunal and ileal solutions did not change significantly during 10 minutes. Also, in the jejunum, no change was observed in the concentration of potassium. There was a slight but significant increase in the ileal concentration of potassium during an absorption test.

During the infusion of the synthetic pentapeptide (at a rate of 4 µg/kg/hr.), the concentration of sodium in the ileum rose slightly. The concentration of potassium in both jejunum and ileum increased significantly when the pentapeptide was infused at this dose rate. During the intravenous infusion of the pentapeptide the concentrations of potassium in the jejunal and ileal lumen after 10 minutes were significantly greater (P < 0.02 and P < 0.05, respectively) than the corresponding final concentrations of potassium in the control experiments. An increase of similar magnitude was observed in the concentration of potassium in the jejunum when the pentapeptide was infused at 8 µg per kg per hour.

**DISCUSSION**

These results show that, when the synthetic gastrin-like pentapeptide was infused intravenously into dogs, the rates of movement of sodium, potassium, and water into and out of isolated segments of small intestine were markedly altered. The intestinal action of the pentapeptide seemed to be selective. Thus in the ileum, but not in the jejunum, the rates of absorption of sodium and water were greatly reduced. In both the ileum and jejunum, when pentapeptide was infused at 4 µg per kilogram per hour, potassium was secreted more rapidly than in control studies. At the higher rate of infusion of pentapeptide (8 µg/kg/hr.), the increase in potassium secretion was maintained in the jejunum but, in the ileum, the rate of secretion returned to control levels. There is no obvious explanation for the failure of the larger dose of pentapeptide to stimulate the ileal secretion of potassium. The colonic handling of water and electrolytes was not affected by the infusion of the gastrin-like pentapeptide.

Recently Gardner, Peskin, Cerda, and Brooks (1967) studied the effect of several gastrointestinal hormones upon the transport of water and electrolytes by everted sacs of hamster intestine in vitro. The introduction of a crude porcine extract of gastrin into the solution bathing the mucosal surface of sacs formed from the distal third of small intestine was followed by a reduction in the net absorption of sodium, chloride, and water. Potassium transport was not affected nor did the remainder of the small intestine show any alteration in the handling of water and electrolytes. The unidirectional flux rates of sodium were studied: the mucosal-to-serosal movement of sodium was reduced when gastrin was instilled into the mucosal solution. The selective action of the gastrin extract upon the ileal absorption of sodium and water is similar to that found in the present study. However, close comparison of the results must be avoided in view of the differences in the nature of the gastrin, in the type of experimental preparation, and in the species of animal.

The changes in the intestinal transport of water

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**TABLE II**

<table>
<thead>
<tr>
<th>Segment</th>
<th>Solution</th>
<th>Control Experiments</th>
<th>Pentapeptide Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>Concentration at t&lt;sub&gt;0&lt;/sub&gt;</td>
<td>150±0.4 (9)</td>
<td>152±0.8 (12)</td>
</tr>
<tr>
<td></td>
<td>Concentration at t&lt;sub&gt;10&lt;/sub&gt;</td>
<td>151±1.0 (9)</td>
<td>154±1.0 (12)</td>
</tr>
<tr>
<td></td>
<td>Mean difference ± S.E. mean</td>
<td>1±0±1.0</td>
<td>2±1.3</td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>0.87</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Ileum</td>
<td>Concentration at t&lt;sub&gt;0&lt;/sub&gt;</td>
<td>152±0.7 (20)</td>
<td>149±1.1 (6)</td>
</tr>
<tr>
<td></td>
<td>Concentration at t&lt;sub&gt;10&lt;/sub&gt;</td>
<td>152±0.6 (20)</td>
<td>151±0.7 (6)</td>
</tr>
<tr>
<td></td>
<td>Mean difference ± S.E. mean</td>
<td>0±0.9</td>
<td>2±0.8</td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>N.S.</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>N.S.</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>Concentration at t&lt;sub&gt;0&lt;/sub&gt;</td>
<td>3.84±0.08 (9/3)</td>
<td>3.98±0.14 (12)</td>
</tr>
<tr>
<td></td>
<td>Concentration at t&lt;sub&gt;10&lt;/sub&gt;</td>
<td>3.99±0.06 (9)</td>
<td>4.41±0.12 (12)</td>
</tr>
<tr>
<td></td>
<td>Mean difference ± S.E. mean</td>
<td>0.15±0.10</td>
<td>0.43±0.19</td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ileum</td>
<td>Concentration at t&lt;sub&gt;0&lt;/sub&gt;</td>
<td>3.92±0.10 (20)</td>
<td>4.00±0.13 (6)</td>
</tr>
<tr>
<td></td>
<td>Concentration at t&lt;sub&gt;10&lt;/sub&gt;</td>
<td>4.25±0.10 (20)</td>
<td>4.90±0.30 (6)</td>
</tr>
<tr>
<td></td>
<td>Mean difference ± S.E. mean</td>
<td>0.33±0.14</td>
<td>0.90±0.35</td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Figures in parenthesis indicate number of experiments.*
and electrolytes may have been brought about by the
direct action of the pentapeptide upon the
mucosal cells of the small intestine. On the other
hand, the observed effects may have been both
secondary and non-specific. First, the reduction in
the rates of absorption of sodium and water and
the increase in potassium secretion, following the
infusion of the pentapeptide, may be secondary to
changes in, for example, intestinal motility. How-
ever, not only is the influence of motility on
intestinal absorption far from clear (Shields, 1964)
but also the alterations in the motility of the small
intestine produced by the pentapeptide are not
marked (Logan and Connell, 1966; Neely, 1967;
Bennett, Misiewicz, and Waller, 1967).
Second, the observed alterations in absorption
and secretion may have been secondary to the
stimulation of gastric secretion of acid. Indeed the
doses of pentapeptide used in this study were those
which Thomas and Forrest (1967), working in this
laboratory, have found to produce the highest
output of acid from denervated Heidenhain gastric
pouches. However, there is no evidence to suggest
that such hypersecretion of acid by the intact
stomach and, particularly, the entry of considerable
quantities of the acid into the small intestine would
per se affect the absorptive and secretory behaviour
of isolated segments of intestine (Miles, Davies, and
Shields, 1965).
Finally the effect of the pentapeptide on the
intestinal transport of water and electrolytes may be
the non-specific action of a foreign peptide.
For this reason the influence of pure antral gastrins
isolated by Gregory and Tracy (1964) upon intesti-
nal absorption should be studied.
These changes in the handling of water and
electrolytes by the small intestine were observed
over three hours, in isolated segments of bowel with
a serosal surface area of 100 cm². From the data
given by Davenport (1961) it can be calculated that
the mucosal area of these segments would probably
represent one-seventh of the mucosal surface area
of the small bowel. If the entire intestine responded
to the pentapeptide in a manner similar to that of
the isolated fistulas the losses of fluid and electrolytes
would be considerable. However, certain additional
points must be taken into consideration. First, the
absorptive ability of the colon was quite unaffected
by the pentapeptide. Because the colon has a reserve
capacity to absorb five to seven times as much
water and salt as it is normally called upon to do
(Shields and Miles, 1965), increased absorption of
sodium and water by the colon may very well
compensate for the observed reduction in absorption
by the ileum. Second, the artificial nature of these
experiments must be borne in mind. Before any
definitive conclusions can be reached upon the effect
of the natural antral hormone upon the intes-
tinal handling of water and electrolytes, the
intestine will have to be studied with its normal
anatomical relationships preserved so that intestinal
mucosa is in contact with food and alimentary
secretions.
The relationship between the results of the
present study and certain aspects of the Zollinger-
Ellison syndrome remains to be discussed. The cause
of the diarrhoea and hypokalaemia which are
additional, occasionally dominating, features of
this syndrome (Zollinger and Grant, 1964) remains
obscure. The pancreatic adenoma is considered to
produce a gastrin-like hormone which stimulates
the hypersecretion of acid by the stomach (Gregory
and Tracy, 1964). Some have attributed the accom-
panying diarrhoea to irritation of the small intestine
by large volumes of acid (Donaldson, Vom Eigen,
and Dwight, 1957; Summerskill, 1959; Rawson,
England, Gillam, French, and Stammers, 1960;
Parker, Soergel, and Ellison, 1963; Miles et al.,
1965). However, it may be that the hormone liberated
by the pancreatic adenoma has a dual effect upon
the intestinal handling of water and electrolytes. In
addition to the secondary irritation of the small
intestine with gastric acid, the gastrin-like hormone
may, as suggested by the present study, act directly
upon the small intestine to augment the secretion of
potassium by the jejunum and ileum, and to reduce
the absorption of sodium and water in the ileum.
The critical experiment remains to study the effect
upon intestinal absorption of a potent extract of
pancreatic adenoma from a patient with the
Zollinger-Ellison syndrome.
A less common form of the syndrome consists of
a non-beta islet cell tumour of the pancreas associ-
ated with profuse watery diarrhoea and severe
hypokalaemia with hypochlorhydria, or even
achlorhydria, and without peptic ulceration (Verner
and Morrison, 1958; Matsumoto, Peter, Schultz,
Hakim, and Franck, 1966). In one patient, pre-
senting such features, the increased secretion of
potassium seemed to be caused by an increase in
the movement of potassium ions into the intestinal
lumen (Espiner and Beaven, 1962)—a response
similar in character to the one observed in the
present study. In this context, it is of interest to note
that increased movement of potassium into the
intestinal lumen has also been observed in other
situations in which hormones seem to be implicated,
for example, following the administration of
aldosterone (Shields et al., 1966), in primary hyper-
aldosteronism (Shields, 1966), and during salt
deplication (Clarke, Miller, and Shields, 1967).
In two patients with diarrhoea and hypokalaemia
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but without gastric hypersecretion and peptic ulceration, assay of the pancreatic adenoma did not reveal any gastrin-like activity (Matsumoto et al., 1966). The mechanism of production of the diarrhoea remains obscure in these cases and the existence of another hormone, originally suggested by Telling and Smiddy (1961), seems most likely. Attempts by experiments in vitro to demonstrate that extracts from these tumours can affect intestinal absorption and secretion of fluid and electrolytes have not met with success (Matsumoto et al., 1966). However, in vitro preparations are not entirely suitable for the study of intestinal transport of water and electrolytes (Shields, 1964).

SUMMARY

The movement of sodium, potassium, and water into and out of isolated segments of jejunum, ileum, and colon of dogs was studied in vivo during the intravenous infusion of a synthetic gastrin-like pentapeptide (I.C.I. 50,123) in doses of 4 µg and 8 µg per kilogram body weight per hour. There was a marked reduction in the rates of absorption of sodium and water in the ileum. In the jejunum and ileum the rates of secretion of potassium were increased when the pentapeptide was infused at a rate of 4 µg per kilogram per hour and, in the jejunum alone, with the higher dose of pentapeptide. The rates of transport of these substances in the colon were not affected by the pentapeptide.

There was a significant increase in the concentration of potassium in the lumen of the small intestine during the infusion of pentapeptide at 4 µg per kilogram per hour.

The action of the pentapeptide is considered to be a direct and specific one on the small intestinal mucosa.

The relationship between the results of this study and the variants of the Zollinger-Ellison syndrome is discussed.

We thank Professor A. P. M. Forrest for his advice on the dosage of the pentapeptide. We are grateful to Dr J. D. Fitzgerald of Imperial Chemical Industries Limited, for the supply of I.C.I. 50,123. This work was supported by a grant from the Medical Research Council to Mr. R. Shields.

We are grateful to Professor C. A. Taylor of the Department of Physics, University College, Cardiff, for granting access to a Stantec Zebra computer on which the rates of net transport and of unidirectional fluxes were calculated.

REFERENCES


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