Wellcome Film Project

Gastrointestinal Hormones

The Scientific Basis of Medicine

Presented by Prof. Iain Gillespie, University of Manchester.

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Introduced by Ian Gilliland.

Produced by Peter Bowen.

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<**Opening titles**>

<**Dr Ian Gilliland to camera**>

Professor Iain Gillespie is Professor of Surgery in the University of Manchester where he went from the Chair of Surgery in the University of Glasgow. Prior to this, he worked with Medical Research Council units both in Glasgow and in Sheffield and as a post-doctoral fellow in the University of Los Angeles. His particular interest is in gastrointestinal hormones and this fascinating field is the subject of today's discourse. Professor Gillespie.

<**Professor Iain Gillespie to camera**>

In the last few years, the hormones of the upper gastrointestinal tract have become quite respectable. Although for many years there was a lot of indirect evidence

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regarding their existence and, indeed, names were prepared for them in anticipation of their identity, it's really just in the last decade that we have come to know precisely the structure and functions of many of these hormones. First of all, there has been the preparation of pure extracts and this has been very quickly followed by the identity of the amino acid sequence of the whole molecule and also, as far as several are concerned, of minimal active small fragments of these molecules. And then, for most of them, this has, in turn, been followed by a synthesis of a variety of active fractions.

We'd like to concentrate today on three of these hormones: gastrin, secretin and the single substance which is now known to have both the effects of gallbladder contraction, that is cholecystokinin, and stimulation of pancreatic enzyme-rich juice, that is pancreozymin.

Now, each has got a clearly defined primary action. Gastrin, the stimulation of acid; secretin, the stimulation of alkaline juice from the pancreas and CCK or cholecystokinin, the ones we've already defined. But interestingly, as more and more work is done on these hormones it is apparent that they, in addition, have a very wide spectra of other biological actions. And as a clinician with a particular hobby interest in these hormones, I, of course, am keen to know whether we can use the knowledge of any of these physiological or pharmacological actions in diagnosis or treatment.

So, let's review these three hormones briefly and here and there stop to consider any possible direct clinical applications of them. And first of all, let's deal with the most famous of all, gastrin – while we know the structure of gastrin thanks to the work of Professor Gregory and Dr Tracy, that it contains 17 amino acids, although physiologically in the circulation there may be several other larger molecules incorporating this 17 amino acid peptide.

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<**Gillespie briefly to camera then narrates over a table with moveable pieces**>

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And our interest in its structure is concentrated on the fact that all the known potent biological actions of gastrin are contained in the crucial C-terminal tetrapeptide sequence, illustrated here. And furthermore, of even greater fascination, is the fact that this almost identical C-terminal structure exists in CCK. The difference being here that tyrosine and its associated sulphate is moved one to the left and methionine substituted at this point. Here is the business end of CCK. And while on this subject, it is tempting to mention the other fascinating substance which has appeared in the skin of certain frogs with, again, an identical C-terminal tetrapeptide sequence, but a slightly different structure, 2 amino acids to the left. And it comes as no surprise that this material, doing goodness knows what in the skin of frogs, has the same range of biological actions as gastrin and CCK.

<**Gillespie to camera, then over graph showing gastrin levels in different disorders of the stomach**>

So much for the structure of these hormones. Let's go back to gastrin and consider its main job, its main action: the stimulation of acid secretion for the stomach. And it is extremely good at it, and it is used clinically, mainly to elicit maximal acid responses, but of what diagnostic use is this? It would be fair to summarise it as being extremely limited at the present day.

Here, for example, is an illustration of the means, that's the solid lines, and the ranges, the shaded areas, in different groups of individuals. Duodenal ulcer, patients with both duodenal and gastric ulcer, gastric ulcer alone, peptic oesophagitis, carcinoma of the stomach and some normals. And although, as everyone knows, patients with duodenal ulcer, either alone or associated with another type of ulcer, have higher levels than other groups of patients, there is such a large overlap of the values of the different groups that the diagnostic discrimination is very limited indeed.

<**Gillespie to camera, then over graph showing the K25 formula**>

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What can we do to improve this diagnostic discrimination, if anything? And there are several experimental approaches to this question. Perhaps we should use combinations of drugs rather than a single drug alone. Maybe we should concentrate less on maximal stimulation and use submaximal or threshold levels. Another approach is to take pepsin output levels into consideration as well as acid and perhaps use simple ratios of one material to the other, or more complicated ratios such as that suggested by Professor Bonfils and his colleagues, the K25 formula.

This seeks to explain what the K25 means. Acid is expressed not simply as milliequivalents but as primary acid output calculated by a formula which involves the use of constants. And the K25 is simply the pepsin output which corresponds to a primary acid output of 25 ml. Well, perhaps this, or other comparable formulae, will give us better diagnostic discrimination but it is fair to say that the diagnostic use we have of acid stimulation tests at the moment is limited.

<**Gillespie to camera, then over graph detailing the role of the vagus in an ulcer patient**>

Well, if we cannot do very well with diagnosis, can we perhaps use gastrin or one of its analogues to help us with some specific clinical surgical questions? I'd like to discuss two. The first is the interesting problem of trying to select individual duodenal ulcer patients for the most appropriate surgical procedure, a topic which has interested surgeons for a long time. And the second is this vexed question of testing for the degree of completeness of vagotomy, again usually in the elective treatment of duodenal ulcer.

Well, the first of these questions has had many approaches and I'd like to mention one just briefly – this has been the possible use of hormones stimulating the gastrointestinal tract to assess the role of the vagus in an individual ulcer patient. And one of the approaches we used some time ago and illustrated here using histamine, but the same message is true of gastrin or pentagastrin, is the so-called medical vagotomy test. This involves for each patient, two tests. On one day, as illustrated here, a straightforward augmented histamine test with histamine and

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antihistamine. On a subsequent day these doses are repeated but, preceding by about 1 hour, there is given an injection of combined hexamethonium and atropine. This results in reduced secretory responses and the shaded area represents the difference between the two tests and was taken as an estimate of how much this individual patient could expect his maximal secretory response to be lowered by the subsequent surgical vagotomy.

<**Gillespie to camera**>

Well, this doesn't work unfortunately and in spite of many modifications to the technique and timing and dosage and drugs of the test, it has not proved of practical value mainly because we are unable to achieve complete pharmacological blockade of the vagus with drugs which are acceptably free of side effects.

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The second question, namely the assessment of completeness of vagotomy is an important one in duodenal ulcer surgery and there is some reason, which we will not enlarge upon, to be dissatisfied with conventional insulin testing. An alternative would be welcome. One possibility that we have been exploring is to see if we could use the alteration in threshold responses to pentagastrin before and after vagotomy operations to make an assessment of completeness.

<**Gillespie over graph comparing quantities of pentagastrin before and after vagotomy**>

This is illustrated by the following study on duodenal ulcer patients both before and after vagotomy operations. What has been done here is to set up an intravenous infusion of minute quantities of pentagastrin starting with 0.008 micrograms per kilogram per minute, and at the end of each hour doubling this dose. Pre-operatively one gets significant stimulation of acid secretion at a dose of 0.064. Following operation, this same dose fails to stimulate secretion and one has to double once, twice, three times before achieving significant acid outputs. This change in the left-

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hand end of the dose response curve is summarised in this next illustration which compares the pre-operative values with the post-operative ones and shows a wide separation between these two curves.

<**Gillespie to camera**>

Perhaps, in fact, the degree of separation may reflect the degree of completeness of vagotomy. Now these are just two possible clinical applications which are perhaps worthy of further assessment at the present moment.

But now let's leave the acid-stimulating property of gastrin and take a brief look at the many other actions which this powerful hormone is known to possess. Let's list these. First of all, it has distinct effects on water and electrolyte secretion, not only in the stomach, as we've already discussed, but also in the pancreas and in the bile. In addition, there are distinct effects on water and electrolyte absorption, for example in the ileum and in the gallbladder. Next, there are effects on various enzymes; the pepsin in the stomach is stimulated as well as acid, although not so powerfully as the acid. And in addition, pancreatic digestive enzymes are also stimulated. There are also effects on other endocrine tissues, for example, insulin and glucagon-releasing tissue and secretin. There is a wide range of effects on the smooth muscle of the entire gastrointestinal tract, from the oesophagus right down to the large intestine and, curiously enough, in addition, in the uterus. Histamine metabolism is also affected by gastrin; there is an increase in the liberation of histamine in the gastric juice in response to gastrin and there is an increase in histidine decarboxylase activity. There is promotion of amino acid uptake both in the stomach and in the pancreas. Metabolic effects include lipolysis and glycogenolysis. Effects on the heart are both inotropic and chronotropic. And finally, there are significant effects on the blood flow in various parts of the gastrointestinal tract – the liver, the small intestine, the pancreas and perhaps also in the limbs. This is an impressive spectrum of actions.

<**Gillespie over illustration of gastrointestinal tract**>

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But on reviewing these, can we use any of them clinically or any of them, at least, worth a clinical trial? Perhaps, to go back to the motility effects for a moment, this illustration summarises the widespread effects of stimulation of motility throughout the gastrointestinal tract and perhaps, therefore, we might be able to use these effects in the clinical condition of paralytic ileus.

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<**Gillespie briefly to camera then over table showing amino acid sequence of secretin, then back to camera**>

Now let's turn to a different hormone, to secretin. Here is the structure of secretin, its amino acid sequence, quite different from that of gastrin and CCK, and the point of interest in showing this structure is that it appears that the entire molecule is required for its biological activity, and that there is no identified active fragment.

Well, its main action, as we know, is to stimulate the flow of alkaline juice from the pancreas. But as time goes on it is apparent that secretin, like the other hormones, has a large spectrum of actions and possibly all the targets which have been shown to respond, one way or another to gastrin, may also respond, though perhaps not in identical fashion, to secretin. It is a powerful alkaliniser of the upper part of the gastrointestinal tract. It liberates not only alkaline pancreatic juice, but bile, the secretion of Brunner's glands. Therefore, there is interest in seeing what effect secretin has directly on the acid secretion of the stomach.

<**Gillespie over graphs and diagrams relating to the effects of secretin, to camera in between**>

And this is shown in an experiment on dogs, here, dogs, stimulated by pentagastrin. And this simply shows that an infusion of secretin reduces profound inhibition. So it is not surprising, knowing that it is capable, in many ways, of neutralising acid which is secreted and now also suppressing further release of acid secretion, it is not surprising that there is clinical trial of secretin in the treatment of duodenal ulcer.

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Ranging over the other effects of secretin, there are interesting motility effects, just as in the case of gastrin. One of these effects of particular interest appears to be a selective action on the musculature at the lower end of the oesophagus where secretin appears to cause distinct relaxation. There is therefore interest in trying secretin in achalasia of the cardia.

<**Gillespie over graphs and illustrations detailing the effects of CCK, to camera in between**>

Likewise, next CCK. As primary actions, already mentioned, stimulation of the gallbladder and stimulation of enzyme-rich pancreatic secretion. But, like the others, it also has a wide spectrum of other interesting biological actions, and this is not surprising in view of the structural similarity between CCK and gastrin. Many of these are shared actions. It also, interestingly enough, is able to inhibit gastric acid secretion, similar to secretin, as is shown by the following experiment where an infusion of CCK causes profound inhibition of the secretory response in pouch dogs to pentagastrin stimulation. So perhaps there might be clinical interest, also, in a trial of CCK.

Going back, once more, to motility effects, CCK has some interesting effects on the smooth muscle tissue of the gastrointestinal tract, and for this hormone there appears to be a selective action on the musculature surrounding the lower end of the common bile duct at the sphincter of Oddi. And if this is the case, perhaps there might be clinical interest in a trial with selected patients with stones obstructing the lower end of the common bile duct.

<**Gillespie to camera**>

Now, so far we have been considering the action of the hormones individually, one at a time. But there is ample reason for interest in the interactions between different groups of hormones because, after all, physiologically they are released into the circulation simultaneously, there is considerable overlap. When considering

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interactions, perhaps the easiest first to look at is the interaction between different pairs of hormones. And there are three possibilities. First of all, the effects of combining two hormones could be simply additive, the effects of one being added to that of the other. Secondly, and we've already discussed examples of this today, one hormone could inhibit the effects of the other. The third possibility is that one would potentiate the other and there are examples of this in the experimental laboratory.

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<**Gillespie over graph showing potentiation between two humoral stimuli of acid secretion**>

Here, for example, is perhaps the first demonstration of potentiation between two humoral stimuli of acid secretion. Now, I am aware that urecholine, a stable cholinester, may not be regarded as a hormone but the same message as shown in this illustration is true for any combination of two quite respectable gastrointestinal hormones; but this is historically the first demonstration and this is why I chose to use it.

This shows, in dogs, that first of all if a small dose of stable cholinester is given, sufficient to give just a small response, and then in addition a small dose of gastrin is added simultaneously – which, of itself, would also give only a small response – that the combination of these two results in grossly increased secretory responses, clearly potentiation for, among other reasons, it greatly exceeds the maximal which you can obtain to either agent alone.

<**Gillespie briefly to camera, then over illustration and graph detailing an experiment into a physiological counterpart for potentiation**>

And that there might be a physiological counterpart for this potentiation in the stimulation of secretion is illustrated in the next simple experiment in dogs.

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This simply shows the very elementary set-up of connecting a filter funnel by means of a rubber tube, to the end of a watertight cannula into a pouch. By this means you can allow gentle distension of the pouch by water or saline running in and out of the pouch at will. By using this simple experimental set-up you can demonstrate potentiation as shown in this illustration. First of all, gastrin was given in a very small dose, repeatedly subcutaneously every 15 minutes, the equivalent of an infusion. And then the pouch was gently distended while the same dose of gastrin continued and the result was greatly potentiated secretory responses. So this is possibly an important physiological example of potentiation.

<**Gillespie to camera, then over illustration detailing what happens when secretin and CCK are combined**>

Well now, potentiation has thus been clearly demonstrated between stimuli of acid secretion. There arises the possibility that a similar process of potentiation may also exist between pairs of inhibitors and we have discussed two inhibitors already – secretin and CCK. Let's see what happens when these are combined.

This last illustration shows, I think, evidence of potentiation. Four experiments were done on the same animal. On each occasion, the stimulus to secretion was a continuous infusion of pentagastrin and this first line simply shows a control experiment with no added inhibitor infusion. On a subsequent day in the same animal, as shown by this next line, the inhibitor infusion was CCK at a dosage of 38 units and this caused just a small amount of inhibition. Again, on another day, as shown by this next line, only secretin was given in a dosage of 19 units. On the fourth and final day, as shown by this line, both drugs were combined but the CCK dosage was only half that of the previous experiment, 19 units. And the secretin dose was likewise half – 9.5 units. And the combination of both of these half doses resulted in profoundly greater inhibition.

<**Gillespie to camera**>

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Now, it is very difficult to prove potentiation statistically, and what we have simply done is use criteria which are accepted to satisfy potentiation between stimuli, turned these upside down to determine the significance of the inhibition and this may not be entirely acceptable, but I am not aware of another more acceptable means of proving the potentiation. We believe that this does demonstrate potentiation. Now, there are likely to be other examples of potentiation of different pairs of inhibitors; these are the only ones that we've studied.

Well, these have just been a few examples of the vast amount of information which has recently been accumulating regarding these known, important hormones of the upper gastrointestinal tract. And as we all know, there has been significant progress in the radioimmunoassay of these and other hormones; this will certainly still further increase our knowledge of the physiological and pharmacological actions of these agents. And in addition, there are waiting in the wings a large number of candidates for recognition as respectable gastrointestinal hormones – there's bulbogastrone and urogastrone, the gastrointestinal inhibitor peptide, vasoactive inhibitor peptide, gastrin itself and many others. There is no doubt that the next few years will see even more rapid progress in our understanding of these fascinating substances.

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