Wellcome Film Project

Prostaglandins: Parts 1 & 2

Part 1, Biochemistry

The Scientific Basis of Medicine

With Professor E W Horton, Department of Pharmacology, University of Edinburgh.

Introduced by Dr Ian Gilliland.

University of London Audio-Visual Centre, 1971.
Made for British Postgraduate Medical Federation.

Produced by Peter Bowen

Black-and-white
Duration: 00:54:52:21

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<Opening titles>

<Gilliland to camera>

Professor Horton is now Professor of Pharmacology in the University of Edinburgh. Prior to that he was Wellcome Professor of Pharmacology in the London University School of Pharmacology. He has done a great deal of original work in kinin and bradykinin and is one of the pioneers in the developing field of prostaglandins, which is the subject of today's communication. Professor Eric Horton.

<Horton, seated, to camera>

Prostaglandins were discovered in the 1930s by the Swedish scientist, Professor U S von Euler. He observed that extracts of human semen contain a substance or substances which contract intestinal and uterine smooth muscle. At that time, it was thought that they originated from the prostate, hence the name prostaglandins. It is now known that the compounds are more widely distributed. They have been isolated from many different animal tissues. In 1960, the first prostaglandins were isolated as pure compounds by Professor Sune Bergström and Dr Jan Sjövall in Stockholm, and with the collaboration of Professor Bengt Samuelsson, they elucidated the full chemical structure of these new compounds. You can see in the diagram that these 4 main groups of prostaglandins are acidic compounds.

<Horton refers to a series of diagrams using indicator stick and narrates over them, interspersed with talk to camera>

They have 2 long chains and they have a 5-membered ring. The different groups differ from each other in the nature of the substituents on the ring, thus prostaglandin Es have a ketonic substituent at the 9-position and a hydroxyl at the 11-position. Prostaglandin Fs have hydroxyls both at the 9- and the 11-position. Prostaglandin As, which are dehydrated forms of Es, lack the hydroxyl in the 9-position to the loss of the molecule of water; they have this 10-11 double bond. And finally, prostaglandin Bs are isomers of prostaglandin As, the double bond having shifted 2 positions into the 8-12-postion.

These four prostaglandins differ in their biological activities, for example, prostaglandin Fs are potent stimulants of isolated smooth muscle but have relatively little action on arterial vasculature. In contrast, prostaglandins A are potent on vascular smooth muscle but have little action on intestinal and uterine smooth muscle. Prostaglandins E are active on both vascular and non-vascular smooth muscle. In general, the prostaglandins B have much less biological activity.

<*To camera*> Now, the origin of these prostaglandins was discovered simultaneously by Professor van Dorp of the Unilever Research Laboratories and Professor

Bergström, who both independently noted the similarity of the structure of these compounds to some of the essential fatty acids.

<*Next diagram*> And in this diagram you can see a general similarity between the C20 unsaturated long-chain fatty acid, arachidonic acid, and prostaglandin E2. It was because of this similarity that the hypothesis was investigated that arachidonic acid might be the precursor of prostaglandin E2, and indeed, this proved to be the case. By the incorporation of a molecule of oxygen across here and another half molecule of oxygen in the 15-position, and ring closure across here, a molecule of prostaglandin E2 can be formed. By a slightly different pathway, but from a common precursor, prostaglandin F2 is also formed from arachidonic acid.

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<*To camera*> Now, arachidonic acid is not present in high concentrations in the normal human diet; our main source of essential fatty acids is, in fact, linoleic acid.

<Horton walks across to chalkboard and writes on it while narrating>

This acid, linoleic, is a C18 acid with 2 cys double bonds. This is converted by enzymes in human tissues and other animal tissues to the compound γ-linolenic acid. This is simply the introduction of an additional double bond. And from there, there is a further enzymic step to dihomo-γ-linolenic acid. This is a chain elongation and we now have a compound C20 with 3 double bonds. By the introduction of yet another double bond into this compound, we have arachidonic acid. Now, this dihomo-γ-linolenic acid is the precursor of another series of prostaglandins, the prostaglandins of the 1 series, which have only 1 double bond in the side chain, in the 13-14-position, and they lack the 5-6 double bond of the E2 and F2 series.

<Horton sits down at desk, then refers to diagrams and narrates over them, interspersed with talk to camera>

Now, all these prostaglandins are widely distributed in animal tissues. This is shown in this diagram here, which indicates some of the sources from which prostaglandins have been isolated and their identification has been shown conclusively by rigorous chemical methods. It's very likely, as shown by many publications that, indeed, prostaglandins are present in practically all animal tissues, but in these other cases, the identification has been considerably less rigorous than in the cases shown here.

You'll see that in addition to semen, the original source of prostaglandins, where they're present in very high concentrations in the case of man, they're also present in the menstrual fluid, in endometrium, in the lung of a large number of species, in brain and a variety of other tissues.

<*To camera*> Now, considerable interest has been generated about the metabolism of these compounds. And the work of the Swedish group, particularly Professor Samuelsson, has shown how these compounds are degraded and removed from the body. If we take prostaglandin E2 in man, this compound goes through a number of stages before it reaches the final urinary excretion product. Two of the most important steps occur in the lung where there are 2 enzymes which metabolise prostaglandins <*next diagram*>: one the 13-reductase reduces this 13-14 double bond, the other the important 15-dehydrogenase oxidises the 15-hydroxyl. This product is considerably less active biologically than the parent prostaglandin. From there, various further steps occur, for example, in the liver beta-oxidation, in this case 2 steps resulting in the loss of the 4-carbon fragment occurs. And then, again in the liver, omega-oxidation resulting in a dioic acid, which in the case of prostaglandin E2 is probably the main urinary metabolite in man.

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<*To camera*> This is shown also in the next diagram <*next diagram*> where we can compare directly the molecule of the prostaglandin E2, and you'll see here the various stages which have occurred: the loss of the 13-14 double bond, the conversion of a hydroxyl in the 15-postion to a ketonic substituent, the loss of 4 carbons here, and the oxidation of the terminal carbon to a carboxyl residue.

<*To camera*> A similar metabolite in human urine has been found after giving prostaglandin F2α, and the only difference between this compound and the human urine metabolite V2 is in the 9-position corresponding to the difference of these two prostaglandins in the parent molecule – the difference between a hydroxyl and a ketonic substituent.

Now, what happens to prostaglandins when we inject them? This has been investigated in animals by using radioactively labelled prostaglandins and one experiment is illustrated in the next diagram. This shows an autoradiograph following the administration of titrated prostaglandin E1 in a mouse <*next diagram*>. Fifteen minutes after the subcutaneous injection of this prostaglandin, the mouse was killed and a sagittal section taken. And here, we've shown by the dark areas, are the areas where the regions where the prostaglandin was located. Label was found in the liver, in the kidney and particularly in the subcutaneous connective tissue. You'll note very little prostaglandin is found in the brain in spite of the fact we know that prostaglandins at this time would be having quite marked effect on the central nervous system. Very little is found in the lungs although we know that the lungs avidly take up prostaglandins on circulation through the pulmonary vasculature. It's interesting to note the high concentration of label in the uterus.

It seems from these experiments, and from others, that when prostaglandin enters the systemic circulation, it is rapidly removed by the lungs where the first two steps in its metabolism occur. The metabolites are then rapidly released into the circulation where they're taken up by the liver and the kidneys particularly, where further metabolism occurs, and then finally excretion, either into the urine or into the lumen of the gastrointestinal tract via the bowel.

<*To camera*> Now, this picture applies both for prostaglandin Es and Fs. A different situation, however, occurs with prostaglandins of the A series, which by and large have been investigated much less. Next slide shows the conversion of prostaglandin As to prostaglandin B. <*Next diagram*> Now, it has been shown that unlike prostaglandins E and F, prostaglandin As are not removed very well from the

circulation by the lungs. On the other hand, again unlike prostaglandins E and F, prostaglandins are metabolised, or at least biologically inactivated, by something in plasma which appears to be an enzyme. And this enzyme, which we have designated prostaglandin isomerase, has now been shown to catalyse the conversion of prostaglandin A to an intermediary between A and B where the double bond is in this 11-12-position. But this compound is rather unstable and rapidly degrades to prostaglandin B by the shift of the double bond into this position.

Now, we have studied some of the characteristics of this isomerase enzyme from plasma. It has a pH optimum of round about 8.5, and you'll notice here that in the absence of isomerase enzyme, that in the presence of base, the reaction from A to B occurs spontaneously. We've measured these conversions by measuring the absorption at 283 nanometres at the representing pH.

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<*To camera*> Now, I'd like to turn to the question of the extraction and estimation of prostaglandins. This is a difficult field because there are so many prostaglandins which are very closely related and which must be separated before adequate identification and estimation can be carried out. The extraction procedure in a simplified form for tissues, and in a modified form for plasma or urine, is shown in this diagram. <*Next diagram*> The tissue may be homogenised in alcohol, then put through some form partition solvent procedure, followed by, for example, silicic acid chromatography, or perhaps reverse phase chromatography, resulting in the separation of broad groups of prostaglandins; although, I've simplified again by omitting any reference to metabolites which, of course, may also be present in the extracts.

Another method of separating prostaglandins is illustrated in the next diagram developed by Dr Anggård in Sweden, an elegant method for the separation of methyl esters of the different prostaglandins. <*Next diagram*> In this case, the ordinate here represents absorbance, or radioactivity in the case of the dotted line. And here the abscissa is fraction number. B-carotene was used as a marker and then you'll see,

as the chromatography on this Sephadex LH-20 proceeds, we have elution of prostaglandins A and B, followed by prostaglandins E and, finally, prostaglandins of the F series.

<*To camera*> Now, following such separative procedures, the only difficulty which remains is to quantitate and to positively identify these prostaglandins. This may be achieved by a combination of gas chromatography and mass spectrometry. It does, however, necessitate the preparation, often on a nanogram scale, of suitable derivatives for gas chromatography. <*Next diagram*> Now, here we have a separation on a gas chromatograph of prostaglandin A1 and B2. These compounds cannot be separated, either by thin layer chromatography or by Sephadex LH-20 or by silicic acid chromatography. And although not shown here, you can also achieve partial separation of prostaglandin A2, which would appear here, and B1, which would be eluted here.

<*To camera*> By combining a gas chromatograph with a mass spectrometer, we can take a mass spectrum as shown in the next diagram at any particular time. <*Next diagram*> Here is a gas chromatic graphic trace resulting from after the injection of a derivative of prostaglandin F2α. Here is the F2α being eluted, and at this point, the mass spectrum was taken, the point at which the maximum amount of prostaglandin was coming off the column.

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<*To camera*> Now, a simplified version, which we refer to as a line diagram, of the mass spectrum of this particular derivative of prostaglandin F2α is shown in the next diagram. First, I will illustrate the molecule itself <*next diagram*>, slightly changed from what you've seen before. First of all, it's the methyl ester and the hydroxyls have now been converted, for the purposes of gas chromatography, to the trimethyl-silyl ethers in each case. The molecular weight of this compound is 584. Now, when this compound reaches the mass spectrometer, where it is bombarded with electrons, the whole molecule becomes ionised. And if the intact molecule in the ionised form passes down to the detector, we see a peak corresponding to the

molecular weight of the compound, 584. On the mass spectrometer, here in the ordinate we represent the percentage abundance of the different peaks, and along here the mass over charge. Now, here you will see 569; 15 less than the parent molecule, corresponding to the loss of a 15 mass units. This may well be the loss of this methyl substituent here, or possibly one of the methyls of the silyl substituent. Now, here 513; 71 different from 584 corresponds to the loss of this side chain, this 5-carbon side chain here. Here, we have 494; 90 difference from the parent molecule corresponding to the loss of this silyl substituent here, or it could be one of these. And, finally, we have 423 which corresponds to 71 plus 90, the loss of 71 here and 90.

<*To camera*> So, in this way, we can, as it were, fingerprint the particular molecule we're looking at and get conclusive identification of the particular compound being estimated. This method is applicable to the nanogram scale and the only limitation is the amount of data that one requires for conclusive identification. In an attempt to illustrate this, this is shown in the next diagram. <*Next diagram*> Here I have plotted, on the ordinate, signal-to-noise ratio of the m over e peaks, and along here, some of the more abundant m over e peaks for the derivative of prostaglandin F2α we were looking at a moment ago. If we have 50 nanograms injected onto the column then the signal-to-noise ratio for all these peaks is, with the exception of this one, always greater than 10. When we go down, however, to 12½ nanograms, the signal-to-noise ratio has become much lower in the case of these peaks. And the identification might then have to depend on the detection of 423, 494 and 513, where the signal-to-noise ratio was still 10 or more.

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<*To camera*> Now, there are other methods of estimation, for example, biological assays using isolated smooth muscle preparations are still widely used. These are highly sensitive but the identification is less conclusive and they provide less information per nanogram than mass spectrometry. Recently, radioimmunoassay procedures have been introduced. These are sensitive and rapid, but they may be considerably less specific than claimed, for example, possible interference by

metabolites must be remembered. In general, these criticisms do not apply to combined gas chromatography-mass spectrometry. By this procedure, and more particularly by multiple ion detection, conclusive identification on the nanogram, or even sub-nanogram level, can be achieved. These techniques are thus applicable to the estimation of the small amounts of prostaglandins released under physiological conditions as I shall show in my next programme.

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Part 2, Pharmacology and Physiology

The Scientific Basis of Medicine

With Professor E W Horton, Department of Pharmacology, University of Edinburgh.

University of London Audio-Visual Centre, 1971.
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Black-and-white

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<Opening titles>

<Horton, seated, to camera. Then refers to a table using an indicator stick and narrates over it>

It is not possible in the time available to refer to all the pharmacological actions of the different prostaglandins or even to discuss all their possible physiological roles. I shall deal first with prostaglandin F2α. It is well known that this compound stimulates the pregnant human myometrium <*table*>, and can be used to stimulate the onset of parturition or induce abortion. I shall describe two other actions of this prostaglandin, namely on the corpus luteum and on the central nervous system, both of which may reflect a physiological role.

<Horton to camera>

Soon after pure prostaglandins became available for investigation, it was discovered that their pharmacological actions were not confined to smooth muscle. They have,

for example, powerful central nervous effects. Some of these are shown in the photograph of an experiment carried out in collaboration with Dr Harvey Mayne.

<Horton narrates over a series of four photographs of chicks at various stages of the experiment>

In this experiment, chicks were injected intravenously with prostaglandin E1 or prostaglandin F2α, 2 and 4 micrograms respectively. One minute after the injection, the chick injected with prostaglandin E1 was heavily sedated and there was a loss righting reflex. In contrast, prostaglandin F2α had little or no sedative effect, but caused this contraction of the extensor muscles of the limb. The effects of E1 lasted for up to sometimes as long as an hour depending on the dose, but the effects were always reversible. And the effects of F2α are of similar duration.

<Horton refers to a series of slides and narrates over them, interspersed with talk to camera>

In this diagram, you can see the response measured from the gastrocnemius muscle to F2α, 1 microgram injected intravenously. About a minute after the injection, there was an onset of muscular contraction which lasted 5 to 10 minutes. This response was obtained in the anaesthetised chicken and showed that the extension of the limb we had seen in the un-anaesthetised animal was probably due to contraction of extensor muscles. Now, in the next slide, we see a similar experiment carried out in a chick with a spinal transection <*graphs*>, showing that the effect can still be produced in the absence of the brain. In the next diagram, you'll see an experiment in which gastrocnemius muscle tension was recorded from both sides, left and right. In response to F2α, 5 micrograms injected intravenously, there was a contraction of both muscles. Then the left sciatic nerve was cut, and a further injection of F2α now elicited a response only on the right side and not on the left.

A control experiment with decamethonium showed that the muscle was capable of contracting. This experiment showed that F2α does not act directly on the muscle or on the neuromuscular junction but almost certainly on the spinal cord.

<*To camera*> In another series of experiments with N L Poyser, we have investigated the luteolytic action of prostaglandin F2α with particular reference to the question of whether this compound is identical with the unknown hormone luteolysin. One method of stimulating the release of luteolysin is to insert foreign bodies into the lumen of the uterus. We carried out an experiment in vitro by inserting polythene tubing into the lumen of the guinea pig uterus and comparing the output of prostaglandin from the distended and the non-distended horn <*next diagram*>. Solvent extraction of the incubation fluid, followed by chromatography and then by gas chromatography and mass spectrometry conclusively proved that F2α is produced by distension though not from the non-distended controls.

The following slides show this evidence. <*Next graph*> Here is the silicic acid chromatograph of the test sample from the extended horn and the control samples. This area here corresponds to the elution time of prostaglandins of the F series. You'll see a large amount of prostaglandin-like F material, as detected by biological assay in the test, compared with very little in the control samples. When we subjected these two fractions to gas chromatography and mass spectrometry, the following results were obtained. <*Next graph*> If we now look at the upper end of the mass spectrum, of the material extracted from the non-distended horn here, you will see that there are four prominent peaks: 361, 382, 437 and 451. These four peaks are also found in the material extracted from the distended horn, here, here, here and here. But, in addition, in the extract from the extended horn, there are many additional peaks: 584, 569, 513, 494, 423, etc., which do not occur in the control sample.

00:35:53:11

Now, the next slide compares the distended horn sample <*next graph*>, which you saw in the previous slide; here we have the 361, 382, 437, 451, but in addition these

other peaks: 584, 69, 53, 494, which correspond to the peaks in authentic prostaglandin F2α: 584, 569, 513, 494, etc. This we regarded as conclusive proof that prostaglandin F2α is released from the guinea pig uterus in response to distension in vitro.

We have obtained similar results following oestrogen treatment on day 6 of the oestrus cycle in guinea pigs. This is another known stimulus to the output of luteolysin. And in the case of the oestrogen experiments, these were carried out in vivo, and we collected samples from the utero-ovarian vein in collaboration with Drs Donovan and Blatchley at the Institute of Psychiatry in London. The question which remains unresolved is how prostaglandin produced from the uterus reaches the corpus luteum. An answer to this apparent mystery may have been achieved by the observation that there is a counter current mechanism between the ovarian artery and the utero-ovarian vein, which I shall demonstrate on the board.

<Horton walks to chalkboard and writes on it while narrating>

In the sheep, at any rate, if we look at the uterine horn, which I can represent diagrammatically with the ovary here with its corpora lutea, and here we have the uterine vein, represented again diagrammatically, and anastomosing with the ovarian vein, and the blood from the uterus flowing in this direction carrying with it any F2α which may be produced. Now, the ovarian artery runs a course, a convoluted course, over this common utero-ovarian vein deeply embedded in it, thus supplying the ovary. And evidence from using radioactive prostaglandin F2α, injected into the uterine vein, indicates that this compound gets across from the lumen of the utero-ovarian vein into the ovarian artery without reaching the systemic circulation at all. And thus reaching the corpus luteum.

This mechanism then seems to account for the local action of the compound luteolysin, which we believe is prostaglandin F2α, on the ipsilateral corpus luteum.

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<Horton sits at desk, to camera>

Now, we've accumulated further evidence in favour of the hypothesis that luteolysin is prostaglandin F2α. In the sheep, we have investigated the output of prostaglandin F2α during the oestrus cycle. And we have found on day 14 of the oestrus cycle as compared with day 7 and other days, earlier days of the oestrus cycle, a significantly different level of prostaglandin F2α. Again, using extraction procedures and separative procedures, as described previously, and then depending upon mass spectrometry for the final identification, we have detected prostaglandin F2α as shown in this slide. You will see that on day 7, there are various peaks which don't correspond to any particular prostaglandin peaks, particularly these which are also seen on day 14 of the cycle. But, in addition, on day 14, the 584, 569, 513, 494, all of which are characteristic of the authentic prostaglandin spectrum. <*To camera*> And this investigation was carried out in collaboration with Dr Bland of the Veterinary College in Edinburgh.

Another investigation, which we're carrying out in collaboration with Drs Heap and Harrison at the Institute of Animal Physiology In Babraham, provides further evidence that prostaglandins are involved in reproduction in the sheep. We've collected blood from the utero-ovarian vein of sheep 2 hours before parturition and have shown the presence, as shown in this diagram, of prostaglandin F2α. <*Next diagram*> Here is the extract below and authentic prostaglandin showing the characteristic peaks. This and the work of other people such as Liggins and Thorburn seems to show fairly conclusively that prostaglandin F2α has a role both in terminating the oestrus cycle in animals and in terminating pregnancy.

I should now like to turn to the actions of another prostaglandin, prostaglandin E1. These are even more numerous than those of F2α. You'll see that prostaglandin E1 has effects on tissues as varied as human platelets, fat, respiratory smooth muscle, reproductive tracts with muscle such as the oviduct. We've already seen the effects on the central nervous system, on water permeability, and on vasculature, the kidney, and gastric secretion. And in the case of these last three effects, the effects are also seen with prostaglandins of the A series.

Now, how can we make any sense of these very varied actions of prostaglandin E1? One hypothesis is that some of the actions, at any rate of this prostaglandin, are mediated by inhibition of the adenyl cyclase system. The next slide shows some of the actions of prostaglandin E1 on this system. <*Next table*> On adipose tissue, for example, where noradrenaline stimulates lipolysis, prostaglandin will inhibit the action of noradrenaline but not of cyclic 3'-5'-AMP, suggesting that the action of prostaglandin E1 is upon adenyl cyclase and the formation of cyclic 3'-5'-AMP. Similarly, on gastric mucosa, pentagastrin-stimulated acid secretion is also inhibited by PG E1. Again, it is thought this is mediated by an inhibition of adenyl cyclase.

A similar argument has been made out for the action of prostaglandin E1 in inhibiting vasopressin on the kidney tubule and on the toad bladder, and again, on the effects of noradrenaline on the cerebellar Purkinje cells. <*To camera*> This effect I might demonstrate on the board.

00:44:53:05

<Horton walks to chalkboard and writes on it while narrating>

If we recall, as Bloom in the States has done, a spontaneously firing Purkinje cell, and then to this Purkinje cell we administer iontophoretically noradrenalin at this point, the firing is inhibited. And then when the noradrenaline injection is stopped, firing returns. Now, if at the same time, during this administration of noradrenaline, we give prostaglandin E1 or E2, like so, then firing returns during the period of the prostaglandin administration. Now, we can get similar effects on firing, similar inhibitory effects with cyclic 3'-5'-AMP. So that if we have a spontaneously firing cell and then administer cyclic AMP, there is inhibition. But if we now, during the course of this inhibition, superimpose E1 or E2, there is no reversal of the cyclic AMP action. This suggests that if the effects of noradrenaline on the firing of the Purkinje cells are mediated by cyclic AMP, then the effect of E1 in inhibiting the action of noradrenaline is probably by an action on adenyl cyclase.

I will illustrate this by a diagram. If you represent adenyl cyclase here acting on the reaction ATP to cyclic AMP, and cyclic AMP would be, in this case – in the case of the Purkinje cells, causing inhibition of firing. In the case of prostaglandin, it inhibits the noradrenaline, which activates the adenyl cyclase, but it does not inhibit the action of cyclic AMP, suggesting that the effects may be inhibitory at somewhere there <*indicates action of adenyl cyclase*> or possibly on the adenyl cyclase. A similar mechanism can be proposed for gastric mucosa, adipose tissue etc.

However, this hypothesis does not apply universally because there are other tissues in which prostaglandins mimic the effects of hormones which exert their effect via adenyl cyclase, for example, the effects of ACTH on corticosterone genesis may be mimicked by prostaglandins. And effects on the thyroid similarly.

However, in those cases where prostaglandin E1 does exert an inhibitory action, it is possible that it is part of a feedback mechanism. It is known, for example, in adipose tissue that when you stimulate lipolysis with noradrenaline there is an output of prostaglandin, and that the amount of prostaglandin produced is sufficient to inhibit the effect of noradrenaline on the adenyl cyclase and thus the formation of cyclic AMP. It is known that prostaglandins are present in the cerebellum and are released from the cerebellar cortex. It has not yet been shown that they're released specifically from the Purkinje cells. But if they are released in response to the action of noradrenaline on the Purkinje cells, then we may postulated that there is a similar kind of arrangement here, that noradrenaline not only stimulates adenyl cyclase but fires off a mechanism which leads to the formation and release of prostaglandins.

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I have drawn here a representation of the adrenergic nerve supplying one of the cells of the spleen. If we stimulate an adrenergic nerve to the spleen, noradrenaline is, of course, released at the transmitter and this leads to the output of prostaglandins from the spleen. Prostaglandins E2 and F2α have been detected. Now Hedqvist, in Sweden, working on the cat spleen, has shown that if prostaglandin E2 is infused intra-arterially in cats to the spleen that the response to nerve stimulation is

diminished and at the output of transmitter is reduced. And he postulates that the prostaglandins produced post-synaptically, in response to the noradrenaline, are acting pre-synaptically to reduce further output of the transmitter. He has evidence from other tissues, notably the vas deferens and the heart, that not only noradrenaline but acetyl choline output in response to nerve stimulation is reduced in response to prostaglandins. It may well be that this is a general mechanism at such synapses.

There is some resemblance, indeed, between some of the actions of prostaglandins of the E series and calcium lack. And this shows up to some extent in the experiments which have been carried out on body temperature regulation. It is well known that 5-hydroxytryptamine injected intraventricularly in the cat causes an increase in body temperature. Furthermore, it has been shown that, in the dog at any rate, 5-hydroxytryptamine injected intraventricularly causes the release of prostaglandins of the E series. Feldberg and Milton have both shown that prostaglandin E1 raises body temperature. And there is an accumulation of evidence that prostaglandin E, on various tissues, exerts its effects by changing calcium and sodium exchange. It is interesting, therefore, that it has been found by Feldberg that calcium lack causes an increase in body temperature as does an increase in sodium in the bathing fluid.

A further point of interest in relation to body temperature is the recent observation of Vane that aspirin and other antipyretic compounds block the synthesis of prostaglandins. And it has now been postulated that the actions of substances like 5-hydroxytryptamine and possibly parogen[?], whose effects are blocked by aspirin, may be exerted via prostaglandin synthesis, and that the aspirin is having an inhibitory action at this point. We know that aspirin does not inhibit the action of prostaglandin E on temperature, so this observation would fit in with this hypothesis.

It may be that this mechanism can apply to a wide variety of sites at which prostaglandins are released. One way of approaching this problem would be to study prostaglandin output under various conditions coupled with the effect of inhibiting prostaglandin synthetase by drugs such as indomethacin.

<End credits>