Thromboxanes: The Power Behind the Prostaglandins?

Previous studies of the roles of prostaglandins as cellular regulatory agents must now be reexamined in light of recent discoveries that are revolutionizing the field of prostaglandin research and may, in fact, overshadow it. New compounds have been isolated that are extremely short-lived but are, in some cases, hundreds of times more potent than prostaglandins. Discoveries of how the new compounds affect cells are already providing answers to some outstanding problems in cell biology. Moreover, the wide-ranging effects of the compounds indicate that they may be of clinical importance in understanding and treating a diverse group of diseases, including heart attacks and asthma.

Prostaglandins, the hormonelike substances found in nearly every kind of animal cell, have been intensively studied for the past decade because of their various effects on physiological processes. They affect male and female reproductive systems, the gastrointestinal system, the cardiovascular and renal systems, and the nervous system. They are released when blood clots, and they are found when tissues become inflamed. However, the exact role of prostaglandins in cellular regulation remains uncertain. In some instances, prostaglandins are synthesized and released at the same time that certain cellular processes occur, but their addition to cells does not cause these processes to occur.

It now appears likely that the functions of the prostaglandins cannot be understood in isolation from the functions of the new compounds: the prostaglandin endoperoxides (PG endoperoxides) and the thromboxanes. The PG endoperoxides are precursors of both the prostaglandins and the thromboxanes (whose name is derived from the fact that they were first isolated from thrombocytes, or platelets, and they contain an oxane ring). However, in many cells, the vast majority of PG endoperoxides are converted to thromboxanes rather than to prostaglandins. The thromboxanes, apparently, are potent cellular regulatory agents.

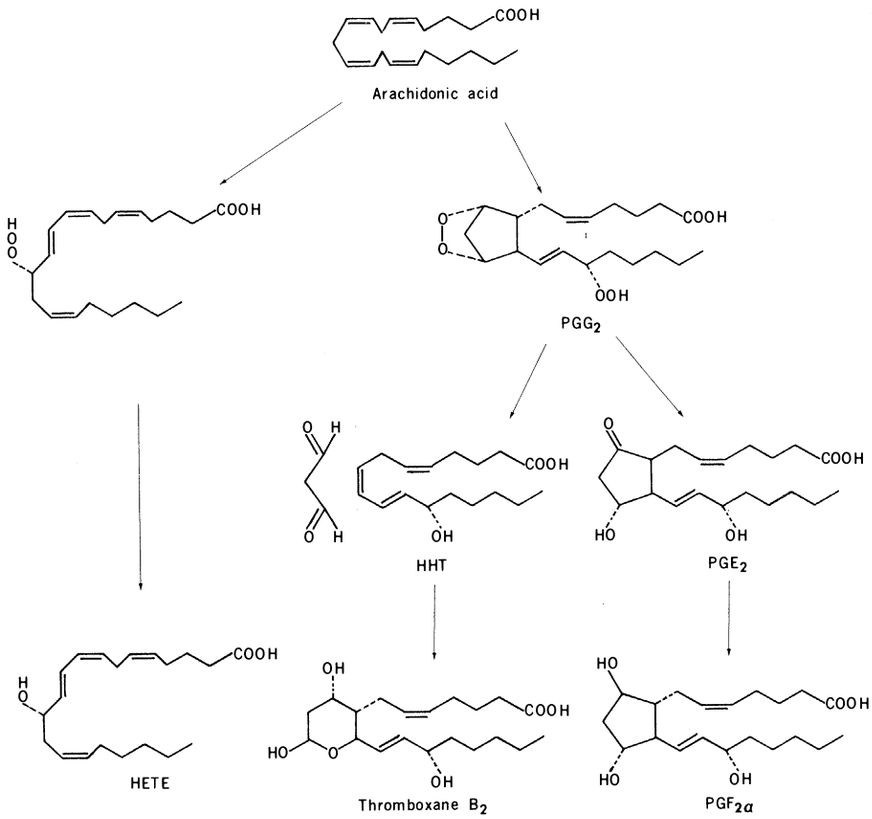
Both the PG endoperoxides and the thromboxanes previously eluded study because they are extremely unstable. The PG endoperoxides have a half-life of about 5 minutes in aqueous solution, and the active form of the thromboxanes has a half-life of about 30 seconds in aqueous solution.

About 1½ years ago, Mats Hamberg and Bengt Samuelsson of the Karolinska Institutet in Stockholm discovered that they could chemically trap PG endoperoxides synthesized in vitro. They stored these compounds in organic solvents and subsequently added them to whole cells. With these techniques, the investigators at the Karolinska Institutet and others have shown that PG endoperoxides can exert dramatic effects on platelets, smooth muscles, and fat cells.

Many investigators now believe that the effects of PG endoperoxides on these cells are actually due to their conversion to the active form of the thromboxanes, namely, thromboxane A_2. Because thromboxane A_2 is so unstable, it is difficult to determine its effects on cells. The cells quickly convert most PG endoperoxides to thromboxane A_2, which is then converted to thromboxane B_2. As far as anyone knows, thromboxane B_2, which is stable, is biologically inert. Hamberg, Samuelsson, and their colleague Jan Svensson, were recently able to chemically trap and characterize this compound. But in order to do experiments with thromboxane A_2, it must be put in an aqueous buffer, where it has a half-life of 30 seconds. Hamberg, Samuelsson, and their associates, however, were able to devise methods to show that thromboxane A_2, rather than PG endoperoxides, affects platelets and rabbit aortas when the endoperoxides are added to these cells.

Studies of the effects of PG endoperoxides and thromboxanes on platelet aggregation, which is part of the blood clotting process, are clearing up some of the mysteries that arose from attempts to explain how prostaglandins are involved in this event. Indirect evidence that prostaglandins affect platelet aggregation followed from two observations: First, prostaglandins E_1 and E_2 (PGE_1 and PGE_2) are released when platelets aggregate. And second, aspirin and indomethacin, which inhibit prostaglandin synthesis, inhibit platelet aggregation. Direct evidence for effects of prostaglandins on platelet physiology, though, was difficult to obtain.

Various groups of investigators showed that, in the presence of agents such as collagen and thrombin, which induce platelets to aggregate, PGE_1 and PGE_2 alter intracellular concentrations of adenosine 3′,5′-monophosphate (cyclic AMP) in platelets.



Transformations of arachidonic acid in platelets. The compound PGG_2 is an endoperoxide. As yet, no biological functions are known for HETE and HHT.

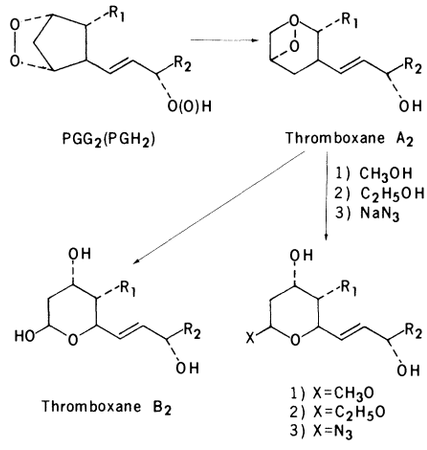
These changes in cyclic AMP concentrations apparently affect platelet aggregation. Aggregation is inhibited by PGE_1, and, although PGE_2 is implicated in aggregation, its effects are not clear. The roles of PGE_1 and PGE_2 are obscured by the fact that neither prostaglandin exerts any effect on platelet physiology in the absence of agents that cause platelets to aggregate.

Hamberg, Samuelsson, and their associates now suggest that PGE_1 and PGE_2 are formed as minor by-products when platelets aggregate and that they modulate the powerful effects of thromboxane A_2. Thromboxane A_2, they find, is the agent that actually causes aggregation. These investigators demonstrated this role of thromboxane A_2 by showing the PG endoperoxides are necessary for aggregation and that if thromboxane A_2, formed from these endoperoxides, is chemically trapped and inactivated, the endoperoxides exert no effects on platelets. They performed three different experiments to show that PG endoperoxides are necessary for platelet aggregation.

In the first experiment, Hamberg and his colleagues added PG endoperoxides to platelets and showed that, in the absence of other compounds that induce aggregation, the platelets aggregate. Then they showed that aspirin and indomethacin act by inhibiting about 95 percent of PG endoperoxide synthesis in human platelets (which explains why they inhibit prostaglandin formation) and that these drugs prevent aggregating agents such as collagen from affecting platelets. However, the effects of aspirin and indomethacin could be overcome if PG endoperoxides were added to platelets. In this case, the platelets aggregate in the presence of the drugs and in the absence of aggregating agents. Finally, they studied the platelets of a patient who had an enzyme deficiency that prevented his platelets from synthesizing PG endoperoxides from their immediate precursor, arachidonic acid. Collagen and other such agents could not induce this person's platelets to aggregate. However, when Hamberg and his associates added PG endoperoxides to a suspension of these platelets, the platelets aggregated.

The addition of PG endoperoxides, like the addition of certain prostaglandins, to smooth muscles causes the muscles to contract. However, the PG endoperoxides are generally more potent than the prostaglandins. This effect is most dramatic in the muscles of the rabbit aorta.

Although the addition of PGE_2 to rabbit aortas causes contractions, Hamberg and his associates find that one of the PG endoperoxides is from 50 to 200 times more active than PGE_2 and that the other endoperoxide is from 100 to 450 times more active in inducing contractions. Moreover, they report that the PG endoperoxides affect rabbit aortas when they are converted into thromboxane A_2 and that thromboxane A_2 is the elusive "rabbit aorta contracting substance" (RCS). This substance was discovered in 1969 by Priscilla Piper and John Vane of the Royal College of Surgeons in London. Piper and Vane found that RCS is released from guinea pig lung tissue under conditions of anaphylactic shock (a violent immunological reaction to large amounts of antibody). However, neither they nor others were able to isolate or identify the highly unstable substance.



Transformations of endoperoxides into thromboxanes.

Endoperoxides have also been shown to affect fat cells and in a manner that clarifies the perplexing reports of the effects of prostaglandins on such cells. Twelve years ago, Sune Bergstrom of the Karolinska Institutet and his associates reported that PGE_1 inhibited fat mobilization induced by hormones acting on adipose tissue. Subsequently, R. W. Butcher of the University of Massachusetts Medical School in Worcester and his associates obtained results that led them to suggest that when hormones stimulate isolated fat cells to break down and release fats, PGE_1 inhibits this process by decreasing the amounts of cyclic AMP in these cells. However, no effects of PGE_1 on the enzyme—adenylate cyclase—that catalyzes the formation of cyclic AMP were ever demonstrated.

Robert Gorman of the Upjohn Company in Kalamazoo, Michigan, together with Hamberg and Samuelsson find that the addition of one of the PG endoperoxides, rather than PGE_1, inhibits adenylate cyclase in hormone-stimulated fat cells. Gorman and his associates suggest that the fat cells may produce PG endoperoxides, and, by implication, thromboxane A_2, in order to temper their response to hormones. The effects of endoperoxides are potent and short-lived, as might be expected of a hormone antagonist that inhibits fat metabolism.

Investigators at the laboratory of R. J. Ho of the University of Miami and others have reported that hormone-stimulated fat cells produce an inhibitor of fat metabolism. However, they have been unable to characterize this substance. Thus the results of Gorman and his associates may help explain these earlier observations.

The direct effect of PG endoperoxides on platelet aggregation, smooth muscle contractions, and fat metabolism give rise to the question of just what are the roles of prostaglandins in these systems. In some cases, such as in platelet aggregation, prostaglandins seem to modulate the effects of thromboxane A_2. In other systems, prostaglandins seem to have the same effects as PG endoperoxides when they are added to cells, although prostaglandins are often not as potent as PG endoperoxides. In these cases, it is possible that, when prostaglandins are added to cells, they shift the biochemical equilibrium of endoperoxide metabolism so that some prostaglandins are converted back into PG endoperoxides which are then metabolized into thromboxanes.

Cells of many tissues convert most of their PG endoperoxides into thromboxanes. This occurs, for example, in platelets, lung cells, and spleen cells. However, Samuelsson reports that kidney cells make mostly prostaglandins from PG endoperoxides and that there is as yet no evidence that vesicular gland cells make anything but prostaglandins from PG endoperoxides. Moreover, PG endoperoxides do not affect the corpus luteum but $PGF_{2\alpha}$ does, according to Samuelsson. Thus the relative roles of prostaglandins, endoperoxides, and thromboxanes are still, for the most part, unknown.

The roles of the PG endoperoxides, thromboxanes, and prostaglandins are of clinical interest. For example, PG endoperoxides cause arteries to constrict and are involved in blood clotting, so they and their derivatives may have a key role in thrombosis. Because of the effects of PG endoperoxides on tissues of the respiratory tract, the group at the Karolinska Institutet suggests that these compounds may be involved in asthma attacks. Samuelsson points out that PG endoperoxides are produced by lung tissues and that they contract smooth muscles and induce labored breathing. Moreover, these endoperoxides are released in large amounts when guinea pig lung tissues are infused with large amounts of an antigen to which they were previously sensitized. This reaction of

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guinea pig lungs is used to model asthma attacks. In order to study the PG endoperoxides and their derivatives, investigators are studying and are synthesizing stable analogs of the PG endoperoxides.

William Lands of the University of Michigan and his associates are studying the kinetics and biochemistry of the enzyme that converts fatty acids to PG endoperoxides. This conversion occurs when the enzyme catalyzes the addition of two oxygen atoms to the fatty acid precursor of endoperoxides. Lands and his colleagues find that the enzyme has three active sites: a site where oxygen binds, a site where the fatty acid binds, and a site where a substance that activates the enzyme binds. According to Lands, the activator is probably an endoperoxide. This indicates that the enzyme is activated by its own reaction product, leading to an explosive rate of synthesis of PG endoperoxides once the reaction begins. Aspirin and indomethacin, Lands finds, inhibit this enzyme by attaching to the fatty acid binding site. Tylenol (*p*-hydroxyacetanilide), on the other hand, binds to the activator site to inactivate the enzyme.

Stable analogs of PG endoperoxides should facilitate studies of their modes of action and may also be of clinical importance. E. J. Corey of Harvard University together with Samuelsson and their associates recently synthesized such a stable endoperoxide analog. They report that this compound is 7.9 times more effective than naturally occurring PG endoperoxides in causing platelets to aggregate, 6 times more effective in causing platelets to release serotonin, and 7 times more effective in causing rabbit aortas to contract. (This means that it is 1450 times more effective than PGE_2 in causing contractions of rabbit aortas.)

Two other stable analogs of PG endoperoxides were synthesized by G. L. Bundy of the Upjohn Company. These analogs have, so far, been shown to be potent constrictors of the bronchii like the naturally occurring PG endoperoxides. Neither Bundy nor Corey and his colleagues have yet determined whether the PG endoperoxide analogs have the same range of biological activity as the naturally occurring endoperoxides or whether they have the same mode of action as the naturally occurring endoperoxides. For example, it is unknown whether they inhibit adenylate cyclase in fat cells. However, as these analogs become more widely available, the prospects for understanding how PG endoperoxides, thromboxanes, and prostaglandins act look promising.—GINA BARI KOLATA

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