Aspirin: New Perspective on Everyman's Medicine

Aspirin is undoubtedly the most widely used medicine in history, but very little has been known about how its beneficial effects are achieved. Earlier this year, however, two groups of British scientists put forward evidence linking aspirin to prostaglandins, a group of biologically active substances that occur in many tissues of the body. What the researchers found was that aspirin and related compounds can prevent the synthesis of prostaglandins by body tissues. The discovery is of interest not only for what it tells about aspirin, but also as an instance of the seemingly ubiquitous involvement of prostaglandins in biological processes. The establishment of a connection between aspirin and prostaglandins may also have practical consequences, such as improved aspirin-like drugs, and may lead to better methods for the prevention of thrombosis (blood clots) and miscarriage.

Aspirin (acetylsalicylic acid) has been part of the medical pharmacopoeia since 1899, and related salicylates had been known much earlier although they were not widely used because of their irritative side effects on the stomach. Current American consumption of salicylates and aspirin combinations amounts to an estimated 20 billion tablets a year. These compounds have three principal therapeutic actions. They reduce the inflammation or swelling that characteristically occurs in injured tissue and in rheumatic joints; they combat fever (antipyretic action) by lowering body temperature; and they relieve pain (analgesic action). No explanation has been advanced for this last effect, but the antiinflammatory and antipyretic effects of aspirin are apparently due to their blocking of the synthesis of specific prostaglandins.

In recent years, prostaglandins have been the subject of intensive research in many laboratories, and reports of new findings involving prostaglandins are appearing with increasing frequency in the biomedical literature. Prostaglandins, in terms of their potential for pharmaceutical applications, have been compared by some to the steroid drugs. Prostaglandin activity has been found in smooth muscle, in the nervous system, in adipose tissue, in the ovaries, in semen, and in the eye. The compounds appear to be present in practically every tissue of the body. They are thought to participate in the body's defenses against infection, in the onset of labor, and in regulatory mechanisms at the cell level.

There appear to be as many as a dozen naturally occurring prostaglandins, all of them long-chain C_{20} compounds that are synthesized by enzyme systems in the body from polyunsaturated fatty acids. The major forms, as well as many artificial analogs, have also been synthesized in the laboratory. A number of substances interfere with the effects of prostaglandins in the body, and others can inhibit their biosynthesis. Recent work at the Royal College of Surgeons (RCS) in London shows aspirin to be a member of this second class of compounds.

There were two RCS research teams, one headed by J. R. Vane and the other composed of J. B. Smith and A. L. Willis, which independently produced the evidence for aspirin's effect on prostaglandin synthesis (*1*). In Vane's experiment, cell-free homogenized material obtained from guinea pig lungs was shown to synthesize two prostaglandins from arachidonic acid, a known precursor. When aspirin and related compounds were added, the prostaglandin production was reduced by an amount proportional to the concentration of aspirin. Working with collaborators, Vane also showed that prostaglandin production from an entire organ, the dog spleen, was inhibited in a similar way. The degree of inhibition varied with the particular prostaglandin whose synthesis was being studied and with the inhibiting compound that was used.

The experiments of Smith and Willis demonstrated prostaglandin inhibition in individual cells, a biological scale intermediate between the cell-free preparation and that of an intact organ. They studied human blood platelets and they found that platelets in the blood of volunteers who had taken aspirin can no longer produce large amounts of prostaglandins. The same effect was present in isolated preparations of platelets.

These findings appear to explain much of the mystery surrounding aspirin's mode of action in the body. Several prostaglandins have been shown to induce fever, and their synthesis and release may stimulate the temperature-regulating mechanisms in the hypothalamus. Thus aspirin may reduce fever by inhibiting prostaglandin synthesis. Anti-inflammatory effects can be explained in the same manner. Since prostaglandins have recently been shown to be involved in inflammation, prevention of their synthesis may be the basis of aspirin's therapeutic prowess against inflammation.

By reducing inflammation, aspirin may also relieve the pain associated with swollen tissue in rheumatism and other disorders. But the more general analgesic properties of aspirin and related compounds are harder to explain. Administration of prostaglandins can induce headache under some circumstances, but according to Vane, there seems to be no evidence for a link between the inhibition of prostaglandin synthesis and analgesic activity.

The RCS findings have led to speculation that the occasional failures of intrauterine contraceptives, which may work by causing local production of prostaglandins, are due to the effects of aspirin. Other scientists, stimulated by the aspirin results, have recently found that several of the sedative drugs commonly prescribed to prevent miscarriage also inhibit prostaglandin synthesis, and they suggest that even better results might be obtained by including aspirin in the drug therapy (*2*). Of particular importance is the RCS finding that aspirin inhibits prostaglandin synthesis in blood platelets; prostaglandins are known to be a factor in causing platelets to stick together, and may therefore be involved in thrombosis (blood clots). Several studies are now under way to resolve the question of whether aspirin may be of use in treating this condition. At the very least, the explanation of how aspirin works has put on a more factual basis man's tendency to treat this substance as a universal panacea.—ALLEN L. HAMMOND

References

1. J. R. Vane, *Nature New Biol.* **231**, 232 (1971); J. B. Smith and A. L. Willis, *ibid.*, p. 235; S. H. Ferreira, S. Moncada, J. R. Vane, *ibid.*, p. 237.
2. A. Tothill, D. Bamford, J. Draper, *Lancet* **1971-II**, 381 (1971).