Prostaglandins and the mechanism of analgesia produced by aspirin-like drugs

S.H. Ferreira, S. Moncada & J.R. Vane

Commentary by

J.R. Vane

By the time this work was published my proposal that the inhibition of cyclooxygenase was the mode of action of aspirin-like drugs had been around for 2 years. Along with Sergio Ferreira, a post-doc from Brazil, and Salvador Moncada, a PhD student from Honduras, we were busy exemplifying the theory and, in particular, were concerned about the role of prostaglandins in pain. This had not been clearly established. They did not cause pain when applied to a blister base but did when injected intramuscularly. Furthermore, Harry Collier and Cyril Schneider (1972) found that prostaglandins injected into the peritoneal cavity of mice elicited a writhing response which could not be blocked by aspirin-like drugs. That fitted in very well!

We subsequently showed that bradykinin in doses which caused nociception when injected into the spleen of a dog also released a prostaglandin-like material into the splenic venous outflow and that this release was blocked by indomethacin, which we used as a standard non-steroid anti-inflammatory drug (NSAID).

Furthermore, Ferreira (1972) showed that prostaglandins produced pain in human volunteers when injected subdermally in high doses but in the concentrations likely to be found in inflammation they mainly produced a long-lasting hyperalgesia or a sensitisation to other chemical or mechanical stimuli. In this paper we reinforced very strongly the idea that a prostaglandin sensitised sensory nerve endings to the nociceptive activity of bradykinin. In those days we used PGE_1 but we now know that the main prostaglandin released in inflammation is PGE_2.

By on-line instantaneous bioassay using the blood-bathed organ technique we showed that there was a continuous basal output of prostaglandins into the venous effluent from the spleen. Injections of bradykinin increased this output in a sharp and transient way. Indomethacin, abolished the basal output of prostaglandin from the spleen and at the same time (in a different series of experiments) reduced the nociceptive activity of bradykinin injected intra-arterially into the spleen. The reduced nociceptive activity was restored by an infusion of prostaglandin E_1.

We proposed, therefore, that prostaglandins accentuate rather than mediate the pain-producing activity of bradykinin.

In this paper Sergio Ferreira began to develop his ideas that part of the analgesic action of aspirin-like drugs is mediated by a central effect. I have always had difficulty with the concept of "partial activity". If part is mediated by central effects, is it 5%, 20%, 80% or what? For me, the application of Occam's razor cuts out more than one site of action and I am comfortable with the idea that all of the shared effects of aspirin-like drugs are brought about simply through one peripheral mode of action. This, of course, does not exclude a particular NSAID from having an additional central effect and such activity has been claimed for diclofenac. However, the discovery by Phil Needleman and his colleagues (Raz *et al.*, 1989) of the second isoenzyme of cyclooxygenase in 1989 has largely removed the need for alternative or additional explanations of the activities of NSAIDs. We can now think of these as being therapeutic through their inhibition of the COX-2 enzyme and damaging to the stomach and kidney through inhibition of the constitutive COX-1 enzyme.

What an enormous clarification the discovery

of COX-2 has brought about! Not only has it provided a much less complex unified theory for the mechanism of action of NSAID's, but in the process has allowed the explanation of the variation in the intensity of side effects between the drugs, on the basis of a varying activity on COX-1 at doses which inhibit COX-2. This work is already leading to the development of much safer NSAID's, which promise to be non-irritating to the stomach.

References

COLLIER, H.O.J. & SCHNEIDER. C. (1972). Nociceptive response to prostaglandins and analgesic actions of aspirin and morphine. *Nature New Biol.*, **236,** 141-143

FERREIRA, S.H. (1972). Prostaglandins, aspirin-like drugs and analgesia. *Nature New Biol.*, **240,** 200-203

RAZ, A. WYCHE, A. AND NEEDLEMAN, P. (1989) Temporal and pharmacological division of fibroblast cyclooxygenase expression into transcriptional and translational phases. *Proc. Natl Acad. Sci. USA*, **86,** 1657-61.