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# ARACHIDONIC ACID METABOLISM, PAIN AND HYPERALGESIA: THE MODE OF ACTION OF NON-STEROID MILD ANALGESICS

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1 Cyclo-oxygenase products such as prostaglandins of the E series and prostacyclin produce the hyperalgesia associated with inflammation.

2 These substances may cause pain and incapacity in some inflammatory conditions.

3 Prostaglandin $E_2$ sensitizes the chemical receptors of afferent pain endings to other inflammatory mediators such as bradykinin and histamine.

4 Unstable intermediates formed in the generation of prostaglandins may also play a role in the production of pain.

5 Drugs such as indomethacin and aspirin which are potent inhibitors of prostaglandin biosynthesis may exert their analgesic effect through this mechanism.

## Introduction

IN recent years the oxidative pathways of polyunsaturated fatty acid metabolism have become the focus of biochemical and pharmacological interest. The identification of prostaglandins (PGs) as stable products derived from unsaturated fatty acids in the development of many diseases has stimulated attempts to define their physiological or pathological role. Ferreira & Vane (1967) have observed that PGs are released from tissues by a variety of stimuli such as chemical or mechanical irritation. Furthermore, the enzymes required to synthesize PGs have been detected in every mammalian tissue so far studied, with the exception of red blood cells. Willis (1969) has found that prostaglandins are present in carrageenin-induced inflammatory exudates collected from rats. Since then, PG release has been described in a wide variety of inflammatory responses in numerous species including man. These investigations led to the theory that PGs are important inflammatory mediators (Vane, 1976).

## Prostaglandins, pain and hyperalgesia

Pain is a characteristic symptom of the inflammatory response, and many anti-inflammatory drugs have mild analgesic properties. PGs from the E series are predominant in inflammatory exudates (Higgs & Salmon, 1979), but Horton (1963) has found that PGE does not produce pain when applied to a blister base. Similarly, high doses of PGs do not cause pain when injected intradermally in rat or man (Crunkhorn & Willis, 1969; 1971). PGs were, therefore, disregarded as pain-producing substances. However, it was discovered that PGE-induced inflammatory lesions became hyperalgesic, or more sensitive to touch (Solomon, Juhlin & Kirschbaum, 1968; Juhlin & Michaelsson, 1969). Moreover, intra-arterial, intravenous or intramuscular injections of PGEs were reported to cause overt pain and headache (Bevegard & Oro, 1969; Karim, 1971; Collier, Karim, Robinson & Somers, 1972; Gillespie, 1972).

Ferreira (1972) has confirmed that subdermal infusions of PGs produce hyperalgesia in man and that unlike histamine or bradykinin this effect is cumulative, depending on the duration of infusion. He has shown that PGs produce a long-lasting sensitization of afferent pain receptors to chemical and mechanical stimulation. Thus, low concentrations of PGs potentiate and enhance the pain-producing properties of bradykinin and histamine. These experiments form the basis of our present understanding of the contribution of PGs to the development of inflammatory hyperalgesia (for review, see Moncada, Ferreira & Vane, 1979).

## Analgesic activity of aspirin-like drugs

A key step in the evolution of the theory that PGs are inflammatory mediators was the discovery that

 

aspirin and other non-steroid anti-inflammatory drugs selectively inhibited PG biosynthesis (Vane, 1971; Smith & Willis, 1971; Ferreira, Moncada & Vane, 1971). This led Vane to propose that inhibition of prostaglandin synthesis explains the therapeutic and toxic effects of these drugs. Aspirin-like drugs are mild analgesics in contrast to narcotic analgesics like morphine. Lim *et al.* (1964) have produced evidence that clearly indicates a central action for morphine and that aspirin has a peripheral site of action. Winder (1959), Randall (1963) and Collier (1969) have reported that irritation or damage to tissues is a prerequisite for the demonstration of the analgesic properties of aspirin. As a consequence these authors have suggested that analgesia is produced by an action against pain-producing mediators released during inflammation. Aspirin does not antagonize the effects of mediators such as bradykinin, histamine or PGs at receptor level. Thus the most likely explanation for aspirin-induced analgesia is prevention of sensitization of sensory nerve endings by the inhibition of PG biosynthesis. This theory is extensively discussed by Moncada *et al.* (1979) and Ferreira & Vane (1979).

## Intermediates in arachidonic acid metabolism

In the first step of PG synthesis from arachidonic acid, unstable cyclic endoperoxides are generated by a dioxygenase reaction with the incorporation of molecular oxygen (Hamberg, Svensson, Wakabayashi & Samuelsson, 1974). These cyclic endoperoxides ($PGG_2$ and $PGH_2$) occupy a pivotal position in the cyclo-oxygenase pathway of arachidonate metabolism. They may be converted to thromboxanes (Hamberg, Svensson & Samuelsson, 1975), prostacyclin (Moncada, Gryglewski, Bunting & Vane, 1976) or the stable PGs. It has been suggested that cyclic endoperoxides are important inflammatory mediators (Kuehl, Humes, Egan, Ham, Beveridge & Van Arman, 1977) and there is evidence that $PGG_2$ causes pain and oedema (Willis, Vane, Kuhn, Scott & Petrin, 1974; Vane, 1976).

An alternative pathway of arachidonic acid oxygenation was described in 1974 after the discovery of a platelet lipoxygenase (Hamberg & Samuelsson, 1974; Nugteren, 1975). This enzyme produces a series of unstable hydroperoxy acids which are then converted to stable hydroxy acids. Fatty acid hydroperoxides are known to cause pain (Ferreira, 1972) and the intensity of pain produced is greater than that induced by either the parent fatty acid, acetylcholine, bradykinin, histamine, or PGs from the E series. It is possible that lipoxygenase plays an important part in the development of inflammatory pain.

## Prostacyclin and hyperalgesia

Prostacyclin is the major cyclo-oxygenase product in blood vessel walls (Moncada *et al.*, 1976) and it is present in inflammatory exudates in comparable concentrations to $PGE_2$ (Higgs & Salmon, 1979). Prostacyclin is a potent vasodilator (Higgs, Cardinal, Moncada & Vane, 1979) and is more potent than $PGE_2$ in producing hyperalgesia in the rat foot (Higgs, Moncada & Vane, 1978; Ferreira, Nakamura & Abreu Castro, 1978). The hyperalgesia produced by prostacyclin does not last as long as that produced by $PGE_2$. Carrageenin-induced hyperalgesia is reduced by aspirin-like drugs administered before or after the inflammatory stimulus. This suggests that prostacyclin is the endogenous mediator of carrageenin-induced hyperalgesia as the longer-lasting effects of $PGE_2$ would not be prevented by late administration of the drug (Ferreira *et al.*, 1978).

In summary, the oxygenation of polyunsaturated fatty acids such as arachidonic acid contributes to inflammatory hyperalgesia by the production of hydroperoxy acids, prostacyclin and $PGE_2$. Furthermore, the mechanism of action of mild analgesics such as aspirin is most likely through the inhibition of the biosynthesis of these substances.

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