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Is Prostaglandin E_2 Involved in the Pathogenesis of Fever? Effects of Interleukin-1 on the Release of Prostaglandins

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Interleukin-1 (IL-1) induces the formation of PGE_2 from monocytes, fibroblasts, muscle cells, and brain tissue by increasing the intracellular concentrations of CA^{2+}; this cation, in turn, activates a phospholipase which cleaves arachidonic acid from either diacylglycerol or a membrane phospholipid. In addition, IL-1 increases the synthesis of cyclooxygenase, as evidenced by the increased conversion of arachidonic acid into prostaglandins after fibroblasts are pre-incubated with IL-1. Evidence is also presented that fever is caused by interleukin-1- induced prostaglandin E_2.

INTRODUCTION

This paper will describe the effects of interleukin-1 (IL-1) on inducing prostaglandin E_2 (PGE_2). In addition, background information on the biochemistry and synthesis of prostaglandins will be presented.

BIOCHEMISTRY OF PGE_2

Prostaglandins are synthesized from arachidonic acid (AA) a 20-carbon fatty acid esterified to many cell phospholipids such as phosphotidylinositol [1]. AA is cleaved by a phospholipase—an enzyme which can be activated by a variety of stimuli such as Ca [2] or hormones [3]. Once released, AA is oxygenated by cyclooxygenase to yield the endoperoxide PGG_2. This compound is then converted to PGH_2 by the substitution of H for OH on carbon number 15. PGH_2 then acts as a substrate for various enzymes, one of which, PGE_2 isomerase, converts PGH_2 into PGE_2, an eicosonoid (i.e., a fatty acid with 20 carbons) which has 1 trans and 1 cis double bond and a five-member ring (carbon 8–12) containing an OH and a carbonyl group [1]. A second OH group is joined to carbon number 15 on the side chain [2] (Fig. 1).

PGE_2 synthesis can be blocked either by steroids (for example, glucocorticoids) or non-steroidal anti-inflammatory drugs (NSAID; e.g., aspirin). Steroids decrease the release of AA from phospholipids, perhaps by interfering with the activity of phospholipase [4,5]. NSAIDs, on the other hand, inhibit cyclooxygenase by interfering with two sites on the enzyme, one of which is a lipophilic region which has a high affinity for non-polar NSAIDs [1,6]. The ability of non-steroidals to inhibit PGE_2 production may explain why these compounds are, under many circumstances, good anti-pyretic agents [7].

EFFECTS OF IL-1 ON PGE_2 PRODUCTION BY VARIOUS CELL TYPES

IL-1 induces many different cell types to produce PGE_2; this phenomenon may represent a general characteristic of IL-1, although it must be stated that certain IL-1 mediated inflammatory effects (e.g., neutrophil degranulation) occur without PGE_2 [8].

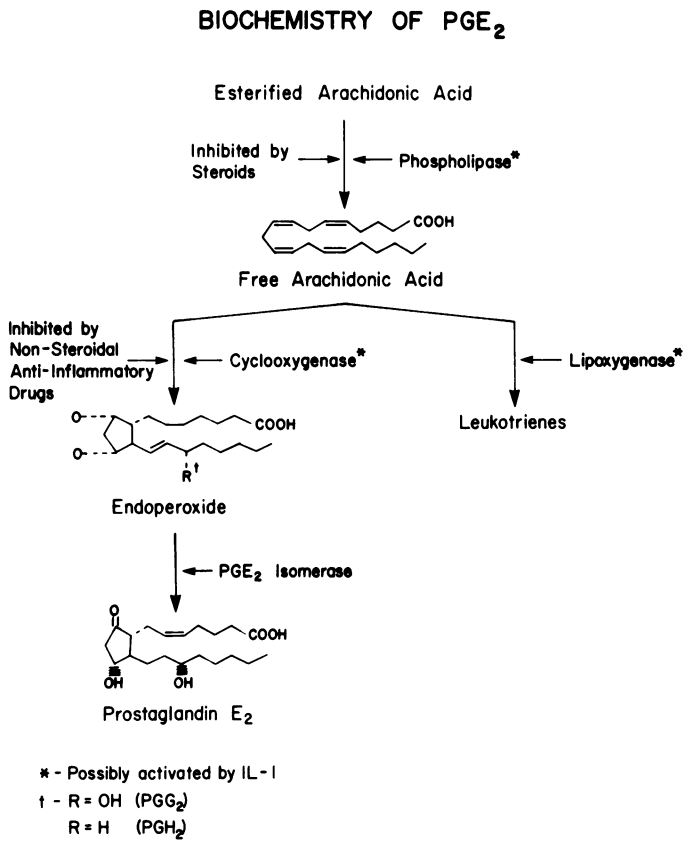

FIG. 1. Biochemistry of arachidonic acid and its derivatives.

Monocytes

When highly purified IL-1 is added to cell cultures of monocytes (1×10^6), PGE_2 levels rise within one hour from essentially 0 pg/ml of supernatant fluid to around 140 pg/ml. This response can be blocked by the addition of the NSAID ibuprofen to the incubation media [9]. The release of PGE_2 by monocytes may be important in immunoregulation, since PGE_2 suppresses the proliferation of certain thymus-derived lymphocytes (T cells) in response to antigens or mitogens [10]. Thus monocytic-derived IL-1 which aids the blastogenesis of mitogen- or antigen-stimulated T cells [11] also stimulates the release of PGE_2 from monocytes; the PGE_2, in turn, then limits T-cell proliferation (perhaps by altering intracellular levels of cyclic nucleotides [12]), a classic negative feedback system.

Muscles

During starvation, a decrease in plasma insulin levels permits the breakdown of muscle proteins to occur. The released amino acids are converted by the liver into glucose to meet the metabolic demands of the central nervous system [13,14]. In addition, acetyl groups and ketones derived from the breakdown of adipose tissue increase during starvation and act as the main source of fuel for the body (during prolonged starvation, the brain switches fuel from glucose to ketones [13]). The use of

ketones as a metabolic fuel allows the muscle tissues to be spared. On the other hand, during infection insulin levels are not suppressed and ketone levels do not rise [15,16,17]. As a result, metabolic demands, which may be higher than normal due to the presence of fever, are met mainly by glucose derived from skeletal muscle amino acids [18]. In addition, there is an increased utilization of amino acids by the liver to synthesize proteins associated with the inflammatory response—the so-called acute-phase inflammatory protein [7,19]. Thus, prolonged infections can cause significant muscle wasting, a common observation in patients with lymphomas and infectious diseases such as tuberculosis [20].

Interleukin-1 appears to be at least one of the molecules involved in muscle proteolysis during infections. Clowes et al. [21] have shown that the proteolytic activity of plasma from patients with trauma or sepsis is 190 percent of controls. The factor responsible for this activity is a peptide with a molecular weight of 4 kd and has been given the name proteolytic initiating factor (PIF). Baracos et al. in a series of experiments demonstrated that highly purified IL-1 increases the rate of proteolysis of rat muscle *in vitro* [22]. The proteolysis (measured by the rate of release of tyrosine into the supernatant media) was accompanied by increased levels of PGE_2; if indomethacin or other NSAIDs were added to the media with IL-1, PGE_2 release and the rate of proteolysis both decreased to control levels. In addition, rate of proteolysis and PGE_2 production in the presence of IL-1 both increased at higher (i.e., 39° vs. 36°C) incubation temperatures. Since IL-1 breaks down *in vivo* into smaller molecular weight molecules (i.e., 4 kd) which retain biologic activity [23], it is quite possible that IL-1 and PIF are at least parts of the same molecule. In fact, trypsin digestion of 15 kd human IL-1 produces a 4 kd product which has almost all of the proteolytic activity of IL-1 and PIF [21,22,24]. Thus it appears that IL-1 is a catabolic molecule which mediates proteolysis via PGE_2.

Fibroblasts

The development of inflammatory lesions seen in rheumatoid arthritis may be due, at least in part, to IL-1, since IL-1 has been identified in effusions from joints of patients with rheumatoid arthritis [25,26]. In addition, monocyte-like cells from synovial explants synthesize IL-1 in response to soluble products [27] released by resident lymphocytes and to immune complexes [28]. Once released, IL-1 induces the synthesis of PGE_2 [29] and collagenase from synovial stellate cells (i.e., fibroblast-like cells found in rheumatoid arthritic lesions [30]). PGE_2 leads to an increase in the synthesis of osteoclast activating factor from lymphocytes [31], while collagenase destroys the matrix of the joint capsule and generates chemotactic factors for monocytes [32,33] and peripheral fibroblasts [34]. Moreover, degranulation products of collagenase stimulate the release of IL-1 from macrophages, resulting in a marked increase in PGE_2 and collagenase levels [35].

Additional experiments with human dermal fibroblasts have shown that IL-1 stimulates the release of PGE_2 from these cells as well. The dermal fibroblasts start to release PGE_2 four to six hours after stimulation and continue to do so for at least 48 hours. Inhibitors of cyclooxygenase (i.e., ibuprofen) eliminate the production of PGE_2 by fibroblasts in response to IL-1; in addition, inhibitors of mRNA translation (e.g., anisomycin) decrease the stimulatory effects of IL-1, indicating that IL-1 induces PGE_2 production by first stimulating the synthesis of new protein [36].

Neuronal Tissue

The ability of IL-1 to initiate fevers appears to be a result of its effect on the CNS rather than the periphery. More specifically, the action of IL-1 seems to be located primarily in the pre-optic anterior hypothalamus (PO/AH) in that microinjections of IL-1 into this area result in fever, while similar injections made into contiguous hypothalamic tissue have little or no effect on body temperature [37,18)]. Furthermore, intravenous injection of IL-1 brings about a change in the discharge rate of thermosensitive neurons; such responses have been consistent with mechanisms of heat-conservation and production of fever [39].

IL-1 appears to bring about a fever by first inducing the production of PGE_2. Briefly, PGE_2 microinjected into the PO/AH produces fever in conscious animals almost indistinguishable from that produced by intravenously injected IL-1 [40]. In addition, endotoxin or IL-1 injected intravenously leads to increased levels of PGE_2 in the third ventricle or cisterna magna [41,42]. Hence a basic working hypothesis is that IL-1 induces PGE_2 synthesis in certain cells (neuronal or non-neuronal—see below) of the PO/AH. This concept is strengthened by the well-documented suppression of IL-1 induced fevers by antipyretics that inhibit the synthesis of PGE_2 from arachidonic acid [43]. Furthermore, PGE_2 synthesis inhibitors have no effect on normal body temperatures. It has been assumed that IL-1 gains access to specific receptors in the PO/AH, where new PGE_2 is synthesized with the concomitant result of fever. However, studies using intrinsically injected ^{125}I-labeled IL-1 have failed to show concentrations of the pyrogen in the anterior hypothalamus [44]. Thus the receptive cells for IL-1 may lie outside the blood-brain barrier (i.e., the organum vascularum lamina terminalis [45]).

Brain minces stimulated *in vitro* with purified IL-1 release PGE_2 within 30–60 minutes after stimulation [46]. Tissue from both the temporal cortex and anterior hypothalamus release similar amounts of PGE_2 in response to IL-1, indicating that receptors for IL-1 are widespread. The NSAID ibuprofen, which reduces fever in humans and is 20 times more potent than acetylsalicylic acid [47], markedly reduced the amount of PGE_2 released by brain minces incubated with IL-1.

Ziel and Krupp, using brain homogenates, showed that IL-1 increases the cerebral prostaglandin synthetase system [48]. In addition, Fagan and Goldberg [49] have shown that brain slices from rats which had been injected with endotoxin (an agent which induces the release of IL-1 *in vivo* and *in vitro*) and which subsequently became febrile released significantly more PGE_2 than brain slices from saline-injected animals. In none of these experiments, however, are the cells which release PGE_2 in response to IL-1 identified. However, Fontana et al. have demonstrated that cultured murine astrocytes (macrophage-like cells which, however, are non-phagocytic and lack Fc and C_3 receptors) release both IL-1 and PGE_2 in response to endotoxin [50]. Thus it may be that astrocytes or other non-neuronal cells in the brain (i.e., dendritic cells) produce PGE_2 in response to IL-1 during the pathogenesis of fever (Table 1).

MODE OF ACTION OF IL-1 IN INDUCING SYNTHESIS OF PGE_2

There is substantial evidence [51] that many agonists exert their effects by influencing the metabolism of phosphoinositides (compounds containing a molecule of glycerol with two esterfied fatty acids and one molecule of inositol with one or more phosphate groups). For example, vasopressin causes a rapid breakdown of phosphoti-

TABLE 1
Tissues Known to Release PGE_2 in Response to IL-1

1. Monocytes
2. Fibroblasts
3. Brain tissue and homogenates
4. Muscle strips

dylinositol 4,5 bisphosphate into diacylglycerol (DAG) and inositol triphosphate [52]. Inositol acts as a second messenger by increasing the levels of intracellular Ca (coming from either internal or external sources [53]), while DAG activates C-kinase, an enzyme which phosphorylates specific regulating enzymes [54,55]. Most of the DAG produced by receptor agonist interactions has arachidonic acid (AA) in its 2 position [56]. Once DAG is formed, AA can be cleaved from the parent molecule by either diacylglycerol lipase [57,58] or by a phosphatidic acid-specific phospholipase after conversion of DAG into phosphatidic acid [59]. The AA, in turn, is converted into prostaglandin by the cyclooxygenase enzyme pathway. The DAG enzymatic pathways require increased intracellular levels of Ca^{++} to operate. There is, however, an alternate route by which AA can be generated. In this system a non-specific, Ca-dependent phospholipase, which has a higher requirement of Ca to operate than the enzymes in the DAG pathway, cleaves AA from various cell membrane phospholipids [60].

Since the enzymes responsible for the cleaving of AA require Ca to be active, it may be that IL-1 exerts its effects, in part, by causing an increase in intracellular levels of Ca. Various experiments have shown that this is indeed the case. For example, calcium ionophores (e.g., A23187) can substitute for IL-1 in inducing PGE_2 production and proteolysis in rat muscle strips [61].

If Ca is removed from the media, A23187 induces significantly less PGE_2 production and muscle proteolysis. In addition, if mepacrine, an inhibitor of Ca-dependent phospholipase, is added to the incubation media, PGE_2 and proteolysis are both decreased in response to A23187. This result indicates that Ca influx induces the synthesis of prostaglandin by first activating a phospholipase.

Besides activating Ca-dependent phospholipases, IL-1 may also increase the activity of cyclooxygenase. Human dermal fibroblasts when pre-incubated with IL-1 converted significantly more AA into prostaglandin when compared to control cells [62]. In addition, microsomal cyclooxygenase activity increases after cells are pre-incubated with IL-1 for 48 hours. If the fibroblasts are pre-incubated in the presence of both IL-1 and protein synthesis inhibitors, there is no increase in AA conversion. Thus, it appears that IL-1 increases the activity of cyclooxygenase by increasing the enzyme's rate of synthesis.

CONCLUSIONS

It seems likely that IL-1 causes fever by first inducing the synthesis of PGE_2. Evidence for this is that injection of PGE_2 into the brain produces a brisk monophasic fever, as does IL-1. Moreover, intravenous injection of IL-1 leads to increases in cerebrospinal fluid PGE_2 which can be correlated with fever height. In addition, NSAIDs eliminate or at least attenuate IL-1 induced fevers but not fevers caused by

injection of PGE_2. Finally, IL-1 stimulates the production of PGE_2 from many cells and tissues studied *in vitro,* including cells located in the brain.

IL-1 may initiate PGE_2 synthesis by increasing internal concentration of Ca, a cation which can activate a phospholipase(s) that cleaves AA from phospholipids or DAG. In addition, IL-1 increases the synthesis of cyclooxygenase as evidenced by the increased conversion of AA into PGE_2 by fibroblasts preincubated with IL-1. This increased conversion is blocked if the fibroblasts are incubated with both IL-1 and a protein synthesis inhibitor, indicating that IL-1 induces the increased synthesis of cyclooxygenase.

The exact role of PGE_2 in fever awaits further experimental evidence. However, with the recent availability of recombinant IL-1 [63], cells responsive to IL-1 in the brain will be able to be identified, as well as their ability to synthesize PGE_2 after IL-1 stimulation.

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