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A study of the pyrogenic actions of interleukin-1α and interleukin-1β: interactions with a steroidal and a non-steroidal anti-inflammatory agent

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1 The pyrogenic effects of intravenously administered human recombinant interleukin-1α (IL-1α) and IL-1β were studied in the rabbit.

2 Both cytokines produced dose-related increases in body temperature. At all doses studied (100–5000 u kg^{-1}) both cytokines elicited a monophasic increase in body temperature, beginning 15 min and reaching a maximum 45 min after administration.

3 A comparison of thermal response index (TRI_2, the magnitude of febrile responses over 2 h obtained by integrating the change in temperature in °C against time in hours) values indicated that IL-1β (500 u kg^{-1}, $TRI_2 = 0{\cdot}69 \pm 0{\cdot}04$, $n = 4$) was approximately 5 fold more potent than IL-1α (2500 u kg^{-1}, $TRI_2 = 0{\cdot}73 \pm 0{\cdot}07$, $n = 4$, all values are means ± s.e.means) in elevating body temperature. ΔT_{max} values for the above doses of IL-1β and IL-1α were 0.60 ± 0.06 and 0.61 ± 0.03 respectively. When IL-1α and IL-1β were heated for 30 min at 60°C prior to administration no biological activity was observed.

4 A cyclo-oxygenase inhibitor, ketoprofen (3 mg kg^{-1}) administered 15 min before either cytokine completely abolished the fever induced by both IL-1α (2500 u kg^{-1}) and IL-1β (500 u kg^{-1}).

5 Intravenous administration of the steroidal anti-inflammatory agent dexamethasone (3 mg kg^{-1}) 1 h before either cytokine attenuated the fever induced by IL-1α (2500 u kg^{-1}) and IL-1β (500 u kg^{-1}).

6 The effects of ketoprofen and dexamethasone on IL-1 pyrogenicity indicate that prostanoids are almost certainly involved in the responses. The different potencies of IL-1α and IL-1β may be related to their relative ability to stimulate prostanoid biosynthesis.

Introduction

Interleukin-1 (IL-1) is a polypeptide with several biological activities regulating host defence and immune responses e.g., stimulation of thymocyte proliferation via induction of IL-2 release, stimulation of B lymphocyte maturation and proliferation, fibroblast growth factor activity and induction of acute phase protein synthesis by hepatocytes. It is synthesized by a number of cell types, particularly monocytes and macrophages upon stimulation with a variety of agents including lipopolysaccharide (LPS), muramyl dipeptide (MDP), phorbol myristate acetate etc. (Dinarello, 1984). It was speculated that these activities did not reside in only one protein, but in a family of proteins. Recently molecular cloning techniques have established that there are two distinct genes in the human genome which encode for two forms of the IL-1 molecule, a form with an isoelectric point (pI) of 5, termed IL-1α and a pI 7 form, termed IL-1β (Auron *et al.*, 1984; March *et al.*, 1985). Both molecules are synthesized as precursors of 31 000 molecular weight, which are post-translationally processed to biologically active proteins of 17 000 molecular weight (Auron *et al.*, 1984; March *et al.*, 1985). Murine (Lomedico *et al.*, 1984), bovine (Maliszewski *et al.*, 1988) and rabbit IL-1 (Furutani *et al.*, 1985) have also been cloned. IL-1α and murine IL-1 appear to be closely related at the level of the amino acid sequence, with 62% homology, whereas IL-1β is only distantly related to either human IL-1α (26%) or murine IL-1 (30%) (March *et al.*, 1985; Auron *et al.*, 1985). Despite the differences in primary structure, the evidence available indicates that murine IL-1, human IL-1α and human IL-1β all bind to the same receptor site (Kilian *et al.*, 1986; Dower *et al.*, 1987) and have similar biological activities (Oppenheim *et al.*, 1986). IL-1 has been shown to stimulate arachidonic acid metabolism, the most consistently observed effect is the increased production of prostaglandin E (PGE) from various cell types including human macrophages (Kunkel *et al.*, 1986) and fibroblasts (Mizel *et al.*, 1981; Newton & Covington 1987). Fever, which is perhaps the most conspicuous component of the acute phase of the immune response, is thought to occur as a result of the actions of PGE_2 on the pre-optic anterior hypothalamus (PO/AH), (Milton 1982; Dascombe 1985). IL-1 is thought to be an endogenous mediator of fever in response to infectious agents and other exogenous pyrogens such as the purified cell-wall components of bacteria (LPS, MDP) and the double-stranded ribonucleic acid, polyinosinic-polycytidylic acid (Dinarello 1984; Rotondo *et al.*, 1987). Recently we have shown that the non-steroidal anti-inflammatory agent ketoprofen and the synthetic glucocorticoid dexamethasone are antipyretic towards LPS, polyinosinic: polycytidylic acid and rabbit endogenous pyrogen/IL-1 (Abul *et al.* 1987; Rotondo *et al.*, 1988).

In this study we investigated the pyrogenicity in rabbits of intravenously administered human recombinant IL-1α and IL-1β and the effects of ketoprofen and dexamethasone on these responses. We have shown that both these agents reduce IL-1α and IL-1β fever.

A preliminary account of this work has appeared in the Journal (Davidson *et al.*, 1989).

Methods

Male Dutch rabbits, weighing 2.0–2.3 kg were lightly restrained in conventional stocks throughout each experiment. To minimize any error in body temperature measurements due to restraint stress, all rabbits were accustomed to the stocks over a period of 5 days before beginning this series of experiments. All experiments were conducted at the same time of day (10 h 00 min–16 h 00 min) and carried out at an ambient temperature of 22 ± 1°C. Body temperature was measured continuously with rectal thermistor probes (Yellow Springs Instruments-401 series), inserted to a depth of 9 cm, which

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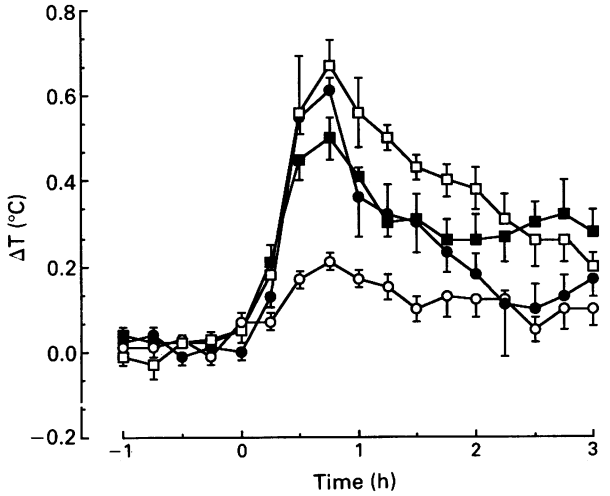

Figure 1 Effect of various doses of interleukin-1α (IL-1α) on body temperature. Rabbits were injected with various doses of IL-1α (u kg^{-1}) at time zero, 500 (○), 1000 (■), 2500 (●) and 5000 (□). Each value represents the mean of the changes in body temperature (°C) from basal for $n = 4$; s.e.mean shown by vertical bars.

were connected to a Jacquet chart recorder. Rabbits were left unhandled after insertion of the probes until body temperature was stable for at least 1 h before any drugs were administered.

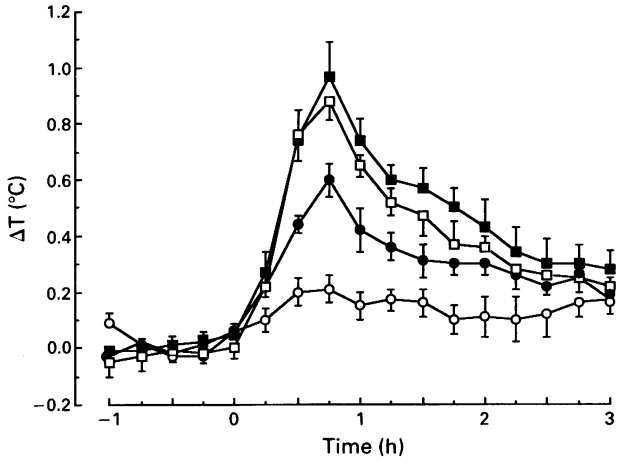

Figure 2 Effect of various doses of interleukin-1β (IL-1β, u kg^{-1}) on body temperature. Details as for Figure 1, except 100 (○), 500 (●), 2500 (□) and 5000 (■) u kg^{-1}.

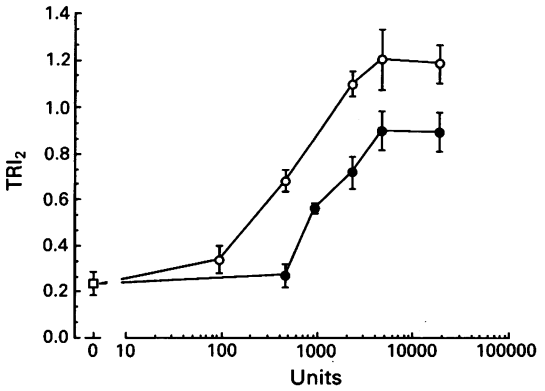

Figure 3 Comparison of the pyrogenicity of interleukin-1α (IL-1α) (●) and IL-1β (○); (□) denotes sterile saline alone. Each point represents the mean of 4 TRI_2 values (calculated as described in the methods section) for 4 rabbits; s.e.mean shown by vertical bars.

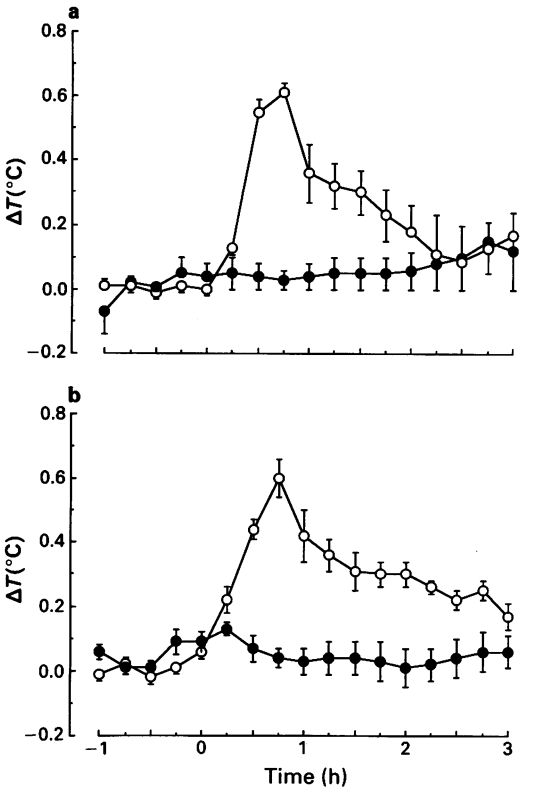

Figure 4 Effect of ketoprofen on interleukin-1 (IL-1) pyrogenicity. Rabbits were injected with 3 mg kg^{-1} ketoprofen (●) or saline (○) s.c. 15 min prior to (a) IL-1α (2500 u kg^{-1} i.v.) or (b) IL-1β (500 u kg^{-1}, i.v.) at time zero. Each value represents the mean of the changes in body temperature (°C) from basal for $n = 4$; s.e.mean shown by vertical bars.

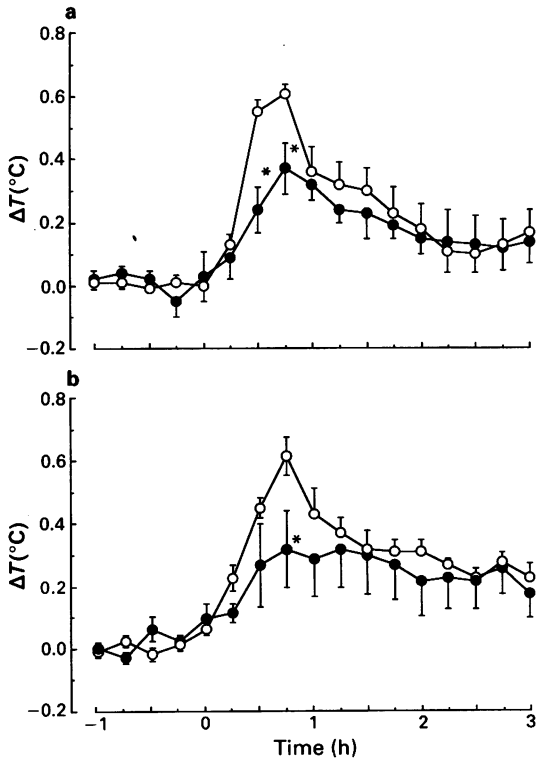

Figure 5 Effect of dexamethasone on interleukin-1 (IL-1) pyrogenicity. Rabbits were injected with 3 mg kg^{-1} dexamethasone (●) or saline (○) i.v. 1 h prior to either (a) IL-1α (2500 u kg^{-1} i.v.) or (b) IL-1β (500 u kg^{-1} i.v.) at time zero. Each value represents the mean of the changes in body temperature (°C) from basal for $n = 4$; s.e.mean shown by vertical bars. *$P < 0.05$, between dexamethasone and saline pretreatments.

Doses of IL-1 were measured in International Reference Units (u) as described by the National Institute for Biological Standards and Control (Hertfordshire, England), from where IL-1α and IL-1β were obtained. One unit of IL-1 is equivalent to 10 pg of protein. Recombinant IL-1, prepared by aseptic techniques, and dexamethasone 21 phosphate disodium (Merck Sharp and Dohme Research Laboratories, Hertfordshire, England) were dissolved in sterile saline (Travenol Laboratories, Norfolk, England). Ketoprofen (May and Baker, Dagenham, England) was prepared by adding warm saline and small amounts of $NaHCO_3$ gradually until it was completely dissolved. In experiments where heated cytokines were administered, the required volume of IL-1 was transferred to sterile Eppendorf tubes and placed in a water bath at 60°C for 30 min. IL-1 and dexamethasone were administered i.v. via the marginal ear vein and ketoprofen was administered s.c. at the nape of the neck. Dexamethasone was administered 1 h and ketoprofen 15 min prior to IL-1. Dexamethasone and ketoprofen were sterilized by passing the solution through Millex-GS 0.22 μm filters immediately before injection. The amount of agent in each dose was adjusted to give an injection volume of 0.5–1.0 ml. The results are expressed as either the change in temperature from basal (ΔT) in °C or as thermal response indexes where the magnitude of the febrile response is determined by integrating the change in temperature (°C) against time (h) to give a thermal response index (TRI) as originally defined by Milton & Wendlant, (1971). Data, expressed as the mean of n experiments $\pm$ the s.e.mean, were analysed by a paired Student's t test. Treatments were randomized, each rabbit acting as its own control and the differences were considered significant when $P < 0.05$.

Results

Various doses of IL-1α and IL-1β were administered i.v. and the febrile response measured for up to 3 h. The response was qualitatively similar with both pyrogens at all doses used, being rapid in onset, typically within 15 min of administration and reaching a maximum after 45 min (Figures 1 and 2). The threshold doses of IL-1α and IL-1β were 500 u kg^{-1} and 100 u kg^{-1} respectively. This produced a maximal rise in rectal temperature (ΔT_{max}) of 0.21 $\pm$ 0.02°C and 0.21 $\pm$ 0.05°C for IL-1α and IL-1β respectively ($n = 4$). Maximal TRI_2 were observed with doses of 5000 u kg^{-1} for both IL-1α and IL-1β (Figure 3) which produced TRI_2 values of 0.916 $\pm$ 0.085 and 1.220 $\pm$ 0.131 respectively showing that IL-1β has greater efficacy than IL-1α. The ΔT_{max} values obtained with 5000 u kg^{-1} were 0.67 $\pm$ 0.06°C and 0.97 $\pm$ 0.12 respectively ($n = 4$, Figures 1, 2 and 3). The magnitude of the febrile response to 20 000 u kg^{-1} of either cytokine was almost identical to that of the response to the same cytokine at the lower dose of 5000 u kg^{-1} and is omitted from Figures 1 and 2 for the sake of clarity but is shown in Figure 3. These data show that IL-1β has a greater pyrogenic action than IL-1α, approximately 5 fold based on the TRI_2 values for 500 u kg^{-1} of IL-1β ($TRI_2 = 0.698 \pm 0.047$) and 2500 u kg^{-1} of IL-1α ($TRI_2 = 0.734 \pm 0.071$). Heating both cytokines to 60°C for 30 min before injection appeared to abolish their pyrogenic actions.

The effect of ketoprofen and dexamethasone on the febrile response to both pyrogens was also studied. Doses of IL-1α (2500 u kg^{-1}) and IL-1β (500 u kg^{-1}) were chosen which gave equivalent increases in body temperature (ΔT_{max} 0.61 $\pm$ 0.03 and 0.60 $\pm$ 0.06 respectively for $n = 4$). Ketoprofen, (3 mg kg^{-1}, s.c.) given 15 min before either cytokine abolished the febrile response to IL-1α and IL-1β (Figure 4). Dexamethasone, (3 mg kg^{-1}) given i.v. 1 h prior to IL-1α and IL-1β attenuated the febrile response to both interleukins and reduced the TRI_2 values to 0.425 $\pm$ 0.098 and 0.450 $\pm$ 0.042 for IL-1α and IL-1β respectively (both $P < 0.02$) and the ΔT_{max} to 0.37 $\pm$ 0.08 and 0.31 $\pm$ 0.12 (both $P < 0.05$) respectively ($n = 4$, Figure 5).

Discussion

Fever is perhaps the most prominent manifestation of the acute phase of the immune response to infection in which the endogenous mediator is thought to be IL-1 (Dinarello, 1984). Many studies of the effects of IL-1 have been carried out with highly purified or recombinant IL-1 from human and other species. However, it still remains unclear why two distinct molecules, IL-1α and IL-1β have evolved which appear to share a broad spectrum of biological activities. Indeed it is not completely resolved whether the activities of IL-1α and IL-1β are the same (Oppenheim *et al.*, 1986).

It has been reported that both recombinant IL-1α and IL-1β are potent pyrogens, however little information is available regarding their relative potencies within the same species. The present study shows that both recombinant human IL-1α and IL-1β are pyrogenic in rabbits when administered i.v., (Figures 1 and 2); however, IL-1β is approximately 5 fold more effective than IL-1α (Figure 3). Dinarello *et al.* (1987) have demonstrated that IL-1α is pyrogenic when injected i.v. into rabbits and Rothwell *et al.*, (1989) have shown that administration of IL-1β into the third cerebral ventricle of rats results in a fever. Work by Stitt & Bernheim (1985) questions the approach of administering IL-1 centrally in that it may produce an artificial situation which may not occur during the normal pathogenesis of fever. It remains unclear whether fever produced by IL-1/EP administered by the intracerebroventricular route is identical in its site and mechanism of action to the fever produced by IL-1/EP administered intravenously and therefore the central administration of IL-1 may not be appropriate for studying its pyrogenic action. Coceani *et al.*, (1988) found that CSF levels of IL-1 were not significantly increased over controls, following i.v. administration, to conscious cats, of a pyrogenic dose of endotoxin or natural human IL-1, indicating blood-borne endotoxin is unable to promote IL-1 generation with the brain and that IL-1 itself cannot cross the blood brain barrier. Also Dinarello *et al.* (1978) injected ^{125}I-labelled IL-1/EP into rabbits which produced a fever but no detectable amounts of radioactivity were found to enter the brain. These observations would suggest that IL-1/EP in the systemic circulation exerts its pyrogenic action outside the CNS.

The increase in body temperature during fever is thought to occur as a result of the actions of prostaglandins of the E series on the PO/AH (Milton & Wendlant, 1970; Milton, 1982; Dascombe, 1985). Non-steroidal anti-inflammatory drugs like aspirin and indomethacin prevent the biosynthesis of prostanoids from arachidonic acid by inhibiting the enzyme cyclo-oxygenase (Flower & Vane, 1974). We report here that the non-steroidal anti-inflammatory agent ketoprofen, which is 12-fold more potent than indomethacin and in the order of 920-fold more potent than aspirin, (Moore, 1985), given s.c. 15 min before either pyrogen, completely abolished the pyrogenic effects of IL-1α and IL-1β. Consequently we propose that IL-1α and IL-1β exert their pyrogenic actions by increasing the level of PGE_2, possibly in the systemic circulation, as peripherally administered agents which inhibit prostanoid biosynthesis such as indomethacin are reported to be unable to cross the blood-brain barrier (Hucker *et al.*, 1966). Rotondo *et al.* (1988), have measured elevations in blood PGE_2 in rabbits, in response to a preparation of rabbit IL-1/EP, which occur simultaneously with increases in body temperature, both of which were completely abolished by treatment with ketoprofen. It is well documented that IL-1 increases the production of prostaglandins of the E series (Newton & Covington, 1987); however, the mechanism by which this occurs remains unknown. In addition we have found that the steroidal anti-inflammatory agent dexamethasone administered i.v. 1 h prior to IL-1α and IL-1β attenuates the febrile response (Figure 5). These results are in agreement with Milton *et al.* (1988) who have shown that, in the rabbit, dexamethasone attenuates both IL-1/EP-induced rises in body temperature and blood levels of PGE_2 and are consistent with the hypoth-

esis that the actions of glucocorticoids are mediated via the induction of lipocortin, a protein inhibitor of PLA_2 (Flower & Blackwell, 1979).

Presumably all the biological effects of IL-1 are receptor-mediated. Human recombinant IL-1α and IL-1β have been reported to bind to the same receptor molecule despite their relatively low homology in primary sequence, suggesting that their tertiary conformation is similar. A number of workers have identified a single high affinity binding protein for both IL-1α and IL-1β with a kd of 10^{-10}–10^{-11} M and a M_r of 80 kDa in human and various other species (see Dower & Urdal, 1987 for review). It is possible that the differences in pyrogenicity of IL-1α and IL-1β described here (Figure 3) may be due to their relative ability to stimulate prostanoid biosynthesis. In a study by Xiao & Levine (1986), recombinant human IL-1α was more effective than recombinant human IL-1β in stimulating arachidonic acid metabolism by primate smooth muscle cells, measured as PGE_2 release, whereas IL-1β was more effective than IL-1α in stimulating arachidonic acid metabolism by rat liver cells. Such diverse activities may be explained by postulating that the IL-1 receptor has different affinities for the two forms of the IL-1 molecule which varies with animal species and/or cell type. Kilian *et al.* (1986) examined the ability of purified recombinant human IL-1α and IL-1β to compete with recombinant [^{125}I]-ILα in receptor binding studies on murine EL-4 thymoma cells. Although human IL-1β was an effective competitor, approximately 2 to 3 fold higher concentrations of human IL-1β were required compared with murine IL-1 or human IL-1α. The dissimilarity between the two IL-1 molecules would suggest that some functions of IL-1 may be mediated by one form and some by the other. One such difference has been reported by Gallagher *et al.* (1987), who found that recombinant human IL-1α but not human recombinant IL-1β supports the growth of Epstein-Barr virus-transformed human B cells, and suggests separate but complementary roles for each molecule as IL-1β was able to synergize with IL-1α to promote cell growth. Recently a receptor for IL-1 has been cloned from murine T cells which binds both IL-1α and IL-1β. Unfortunately no information is available as yet on the signal transduction mechanism of the receptor (Sims *et al.*, 1988). Once available this may shed more light onto the relative functions of IL-1α and IL-1β.

It was also shown in the present study that heating IL-1α and IL-1β resulted in loss of pyrogenicity. This would concur with Xiao & Levine (1986), who have reported loss of PGE_2 stimulating activity when the two cytokines were heated. Heating presumably would lead to loss of the tertiary structure of both molecules, hence they would be unable to bind to their receptor. This together with the fact that no tolerance to IL-1α and IL-1β was observed throughout this series of experiments confirms that the pyrogenic activity shown here of both cytokines, was not due to endotoxin contamination.

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