J. Pharm. Pharmacol. 1984, 36: 644
Communicated April 27, 1984

Contribution of LTB_4 to leukocyte migration in inflammatory lesions

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In a recent paper in the Journal (35: 808–813) Salmon et al concluded that the inhibition of cell migration into carrageenan impregnated sponges by anti-inflammatory drugs is not related to inhibition of prostaglandin synthesis. This conclusion was based on the evidence that aspirin did not influence cell influx at doses which block the formation of PGE_2 and that anti-inflammatory drugs, such as indomethacin and flurbiprofen, inhibit cell migration only at doses higher than those required to inhibit cyclooxygenase to a comparable extent. However, in their desire to ascribe a prominent role for LTB_4 as a mediator of leukocyte recruitment in this model, the authors fail to explain why reduction of cell migration by intermediate doses of indomethacin and flurbiprofen occurred despite enhancement of LTB_4 synthesis.

While accepting that LTB_4 contributes to cell recruitment into inflammatory lesions, we concur with the statement that oxidation products of arachidonic acid are not the only mediators involved: others such as histamine, kinins, complement components and PAF acether may also participate. Indeed, Salmon et al demonstrated that cell migration continues when both prostaglandin and leukotriene synthesis are totally blocked by BW 755C.

The data of Salmon et al are not inconsistent with prostaglandins acting synergistically with leukotrienes and/or other mediators, in accordance with the two mediator hypotheses of Williams (Williams & Peck 1977; Williams 1979; Williams et al 1983) and of Issekutz & Movat (1982) which are based on evidence for the potentiation by prostaglandins of various vascular permeability and cell migration increasing mediators. Indeed, Bray et al (1981) demonstrated that the effects of LTB_4 on vascular permeability can only be observed in the presence of a vasodilator such as PGE_2 and it is likely that a similar situation exists with regard to cell migration. According to this hypothesis, cell migration might be inhibited as a result of a reduction in synthesis of either prostaglandins or leukotrienes or both. We feel that most of the data reported by Salmon et al are consistent with the view that the reduction in cell accumulation shown by BW755C, dexamethasone, indomethacin and flurbiprofen is explicable in terms of a reduction in prostaglandins rather than LTB_4, particularly since the first two and last two compounds have opposite effects on LTB_4 synthesis.

The data reported for the effects of aspirin require explanation. Sultan et al (1978) have reported that, under certain conditions, the migratory potential of leukocytes from aspirin-treated rats is actually increased. Such an effect might offset the expected inhibition of migration associated with inhibition of prostaglandin synthesis by rendering the cells more responsive to whichever chemotactic stimulus is present and may explain why aspirin is a relatively weak anti-inflammatory drug.

In conclusion, we feel that Salmon et al have overstressed the contribution of LTB_4 to leukocyte migration into inflammatory lesions and suggest that other mediators including prostaglandins should be given greater prominence when attempting to understand physiological processes and considering the action of anti-inflammatory drugs.

REFERENCES

Bray, M. A., Cunningham, F. M., Ford-Hutchinson, A. W., Smith, M. J. H. (1981) Br. J. Pharmac. 72: 483–486

Issekutz, A. C., Movat, H. Z. (1982) Am. J. Pathol. 107: 300–309

Sultan, A. M., Dunn, C. J., Willoughby, D. A. (1978) Eur. J. Rheumatol. Inflamm. 1: 291–294

Williams, T. J. (1979) Br. J. Pharmac. 65: 517–524

Williams, T. J., Peck, M. J. (1977) Nature 270: 530–532

Williams, T. J., Jose, P. J., Wedmore, C. V., Peck, M. J., Forrest, M. J. (1983) Adv. Prostaglandin, Thromboxane and Leukotriene Res. 11: 33–37