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Leukotriene B_4 (isomer III): biological activities of synthethic and biologically derived preparations

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Leukotriene B_4 (isomer III), generated enzymatically in leucocytes from arachidonic acid via 5-hydroperoxy-eicosatetraenoic acid and leukotriene A_4, may be isolated by a combination of solvent extraction, silicic acid chromatography and reverse phase high pressure liquid chromatography (Borgeat & Samuelsson 1979a, 1979b). The exact stereochemistry of the leukotriene has now been proved by total synthesis as 5(*S*),12(*R*)-dihydroxy-6-*cis*, 8-*trans*,10-*trans*, 14-*cis*-eicosatetraenoic acid (Corey et al 1980). The activities of the biologically derived preparation have been investigated using material obtained from supernatants derived from leucocytes exposed to the calcium ionophore A23187 (Ford-Hutchinson et al 1980; Palmer et al 1980; Goetzl & Pickett 1980). The most prominent activities are the stimulation of the movement (chemokinesis and chemotaxis) and aggregation of polymorphonuclear leucocytes (PMNs) and the substance is equipotent on a molar basis in vitro with established cytotaxins such as the complement derived peptide C5a and the synthetic peptide F-met-leu-phe (Ford-Hutchinson et al 1980; Bray et al 1981).

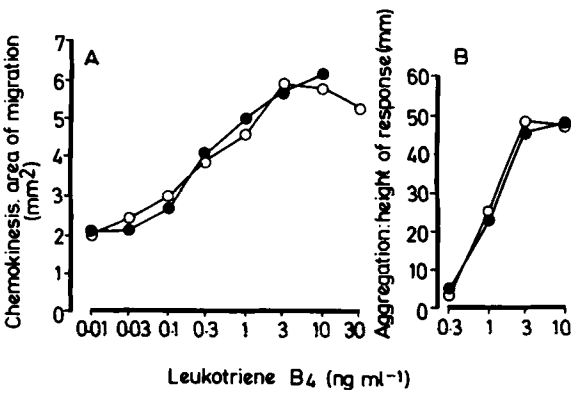

FIG. 1. In vitro effects of synthetic and biologically derived leukotriene B_4 (isomer III) upon A, human PMN chemokinesis and B, rat PMN aggregation. A. Human peripheral blood PMNs were cultured for 1·5 h at 37 °C in the presence of increasing doses of either biologically derived leukotriene B_4 (isomer III) (●) or synthetic leukotriene B_4 (○). Each point represents the mean of 6 replicates (s.e.m. always <7·0% of the mean). Ordinate: chemokinesis: area of migration (mm^2). B. Rat peritoneal PMNs were exposed to increasing doses of either biologically derived leukotriene B_4 (isomer III) (●) or synthetic leukotriene B_4 (○). Each point represents the mean of 5–10 replicates (s.e.m. always <10% of the mean). Ordinate: aggregation: height of response (mm). Abscissa: dose of leukotriene B_4 (ng ml^{-1}).

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We have now made a direct comparison of the biological activities of a preparation of leukotriene B_4 (isomer III) obtained by total synthesis with the purified material obtained from rat peritoneal PMNs exposed to ionophore (Ford-Hutchinson et al 1980). The effects of both preparations on the aggregation of rat PMNs (Cunningham et al 1980) and on the chemokinesis of human PMNs in vitro (Smith & Walker 1980) are shown in Fig. 1. There are no significant differences between the two preparations of the leukotrienes, the ED50s of the synthetic and biologically derived leukotriene being 1·0 ng ml^{-1} and 1·05 ng ml^{-1} respectively for the aggregation assay and 235pg ml^{-1} and 250pg ml^{-1} for the chemokinesis measurement. These results demonstrate first, that the biologically derived material possesses identical biological activities to the synthetic leukotriene and secondly, that the biological properties previously reported from the biologically derived material are therefore due to the presence of 5(*S*),12(*R*)-dihydroxy-6-*cis*, 8-*trans*-10-*trans*, 14-*cis*-eicosatetraenoic acid (Ford-Hutchinson et al 1980; Smith et al 1980).

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