The action of anti-inflammatory drugs in two models of inflammation

Two experimental models of inflammation used for testing anti-inflammatory activity of new drugs are carrageenan oedema and dextran anaphylactoid reaction in rat paws. While testing the sensitivity of Wistar rats to carrageenan (lamda, Marine Colloids Inc.) and to clinical dextran (molecular weight 110 000), it was found that animals from the ASH colony responded equally well to 1 mg of either agent subcutaneously, those from the Tuck colony responded better to dextran than to carrageenan, and those from the LSH colony responded to carrageenan but not to dextran. Regardless of the colony of rat, non-steroidal anti-inflammatory drugs were active against both agents. However, when the sensitivity to carrageenan and to dextran by the subcutaneous and intradermal routes was tested in the same animal discrepancies were found and those required elucidation.

Groups of at least 6 ASH female rats were injected intradermally with carrageenan, dextran or Tyrode solution into several spots on the shaved skin of the back. Immediately afterwards, a subcutaneous injection of carrageenan or dextran was made into the right hind paw and the increase in paw volume was recorded on a volume differential meter over 6 h. Whereas 1–3 intradermal injections did not modify any of the responses in the paw, the simultaneous intradermal injection of 9 doses of carrageenan significantly reduced (by more than 50%) the paw response to carrageenan in the later phases of inflammation (Fig. 1) without changing the response to dextran. In contrast, 9 intradermal doses of dextran or Tyrode solution were without effect on either subcutaneous carrageenan or dextran. Therefore, when multiple doses of carrageenan were injected intradermally, a blood-borne factor was acting as an anti-inflammatory agent against subcutaneous carrageenan but not against subcutaneous dextran. There are major differences between the carrageenan and dextran responses. It is known, for example, that the dextran reaction requires higher doses (up to 4-fold) of non-steroidal, anti-inflammatory drugs to produce inhibition than does the carrageenan oedema; hence, it may be that insufficient of the blood-borne factor was produced by multiple doses of intradermal carrageenan to inhibit the subcutaneous dextran response. Also the dextran reaction involves 5-hydroxytrypta-

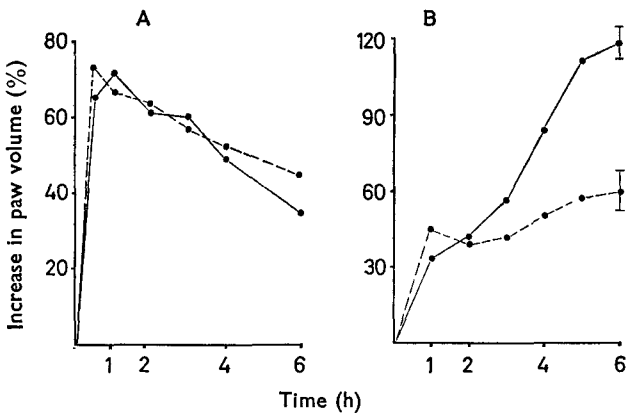

FIG. 1. Percentage increase (± s.e.) in paw volume of ASH rats injected with subcutaneous dextran (A) and carrageenan (B). Continuous lines are control responses in rats injected subcutaneously with 9 intradermal doses of Tyrode solution. Broken lines are responses in rats receiving 9 intradermal doses of carrageenan simultaneously with the subcutaneous dose of dextran or carrageenan. Note that carrageeman intradermally markedly reduces the response to subcutaneous carrageenan but not to dextran.

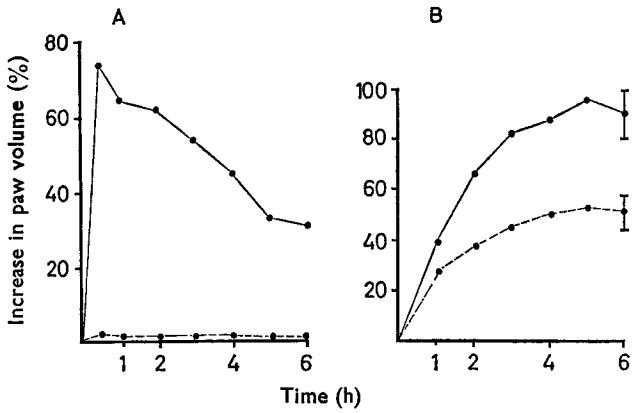

FIG. 2. Percentage increase (± s.e.) in paw volume of ASH rats injected with subcutaneous dextran (A) and carrageenan (B). Continuous lines are control responses in rats previously injected subcutaneously with 8 doses of Tyrode solution over 4 days. Broken lines are responses in rats made refractory to dextran (8 doses). Note that subcutaneous carrageenan still produces a response (though reduced) in rats made refractory to dextran.

mine and histamine (Parratt & West, 1957) whereas the later stages of the carrageenan oedema involve kinins and prostaglandins (Di Rosa & Willoughby, 1971).

The difference between the dextran and carrageenan responses was further demonstrated when antagonists were used. Anti-inflammatory drugs such as aspirin (100–600 mg kg^{-1} orally) and amino acid esters such as phenylalanine heptyl ester (25–100 mg kg^{-1} i.p.) produced dose-dependent inhibitions of both carrageenan and dextran responses in rat paws, but the dipeptide phenylalanyl-phenylalanine (300 mg kg^{-1} i.p.) did not inhibit dextran yet it was active against carrageenan (Thomas & West, 1973).

When rats were made refractory to subcutaneous dextran (by injections twice daily over 4 days), they still responded to subcutaneous carrageenan though this was reduced to about 50% of the control value, from the second hour onwards (Fig. 2). The reduced carrageenan response was susceptible to treatment by anti-inflammatory agents such as aspirin, phenylalanine heptyl ester, and phenylalanyl-phenylalanine.

These results suggest that the use of the dextran anaphylactoid reaction in rats for the testing of anti-inflammatory drugs has certain limitations, and that a blood-borne factor such as a dipeptide (McArthur, Dawkins & Smith, 1971) is released in carrageenan inflammation and exerts an anti-inflammatory action.

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