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The enhancement of dextran anaphylactoid reaction in the rat by sodium salicylate

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Sodium salicylate, like aspirin and indomethacin, is a recognized potent non-steroidal anti-inflammatory agent. However, in animal experiments, it prevents the gastric lesions produced by aspirin without modifying that drug's anti inflammatory effects. It also inhibits the marked gastrointestinal actions of indomethacin, when given either simultaneously (Ezer et al 1976) or up to several hours later (Ezer & Szporny 1981). This protective action of sodium salicylate may be the result of the inhibitory effect of aspirin and indomethacin on prostaglandin synthetase being blocked, as sodium salicylate itself has little effect on that enzyme locally.

Recently, sodium salicylate was found to be an effective adjuvant for the rectal absorption both of insulin and of heparin (Nishihata et al 1981). The enhanced transport of these two drugs across the rectal mucosa is still not understood but the mechanism of action of sodium salicylate appears to be different from that of surfactants like sodium lauryl sulphate which damages the tissue and produces bleeding.

The aim of the present study was to determine the effect of different doses of sodium salicylate on some animal models of inflammation in rats. For example, the dextran anaphylactoid reaction in rats, resulting from the release of histamine and 5-hydroxytryptamine, consists of erythema, pruritus, and gross oedema of the extremities; the reaction mimics many human intolerances to drugs and the early vascular phase of the acute allergic reaction. In the rat it is genetically controlled (Harris et al 1963), just as are many allergic states in man. Doses of sodium salicylate above 100 mg kg^{-1} reduce the reaction (Warne & West 1978), as do aspirin and indomethacin, but the effects of much smaller doses of salicylate have not been studied in detail.

Two types of rat were used—one that responds to the first intraperitoneal injection of dextran (the reactor or R rats obtained from the Tuck Wistar colony) and one that does not (the non reactor or NR rats obtained from the NELP colony). Groups of 5 male animals (250–300 g) were injected with clinical dextran (Intradex, molecular weight 110 000) either intraperitoneally (100 mg kg^{-1}) or locally into a hind paw (50–500 μg). In each case, the percentage increases in hind paw volume were determined on a volume differential meter over 5 h and 60 min, respectively. Each volume shown in the Figures is the mean $\pm$ s.e.m. In other experiments, sodium salicylate was dissolved in 0·9 % NaCl (saline) and administered together with the dextran or 30 min before or after it.

Fig. 1 shows the result for the simultaneous intraperitoneal administration of dextran and sodium salicylate in R rats. The dose of dextran used (100 mg kg^{-1}) was selected so that the anaphylactoid reaction was submaximal. However, the presence of a low dose of sodium salicylate (30 mg kg^{-1}) clearly potentiated the onset of the reaction, the peak value attained, and the duration of the response. The values at all times were significantly raised ($P < 0.05$). This unexpected result suggests enhanced absorption of dextran from the peritoneal cavity (like that reported for insulin and heparin from the rectum). A similar result was obtained when sodium salicylate was injected 30 min after the dextran treatment, but there was no enhancement when it was administered 30 min before. For the dose of dextran used (100 mg kg^{-1}), enhancement was optimal with 30 mg kg^{-1} sodium salicylate, being less with 15 or 60 mg kg^{-1}. NR rats do not produce an anaphylactoid reaction with dextran, and sodium salicylate failed to break down this resistance at all dose levels tested.

When administered locally into one hind paw of R

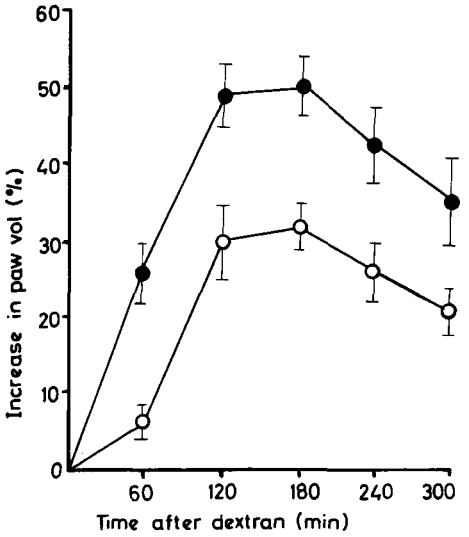

FIG. 1. Effect of dextran (100 mg kg^{-1}, intraperitoneally) on the hind paw volume of R rats alone (○) and in the presence (●) of sodium salicylate (30 mg kg^{-1} intraperitoneally). Groups of 5 rats used for each determination. Vertical lines represent s.e.m. (n = 3). Note the enhancement of all stages of the dextran reaction.

rats, sodium salicylate again enhanced the dextran reaction. The response was optimal when a mixture of a threshold dose of dextran (50 μg) and sodium salicylate (30 μg) was used. This is shown in Fig. 2, together with the negative result using a smaller dose of sodium salicylate (15 μg). The higher dose clearly potentiated the onset of the reaction, the peak value obtained, and the duration of the response. At 60 min, paws injected with the mixture of dextran and sodium salicylate were grossly cyanosed. Even higher doses (90 μg and more) of sodium salicylate were much less effective in producing enhancement. Hind paws of NR rats did not respond to local dextran, even in the presence of sodium salicylate.

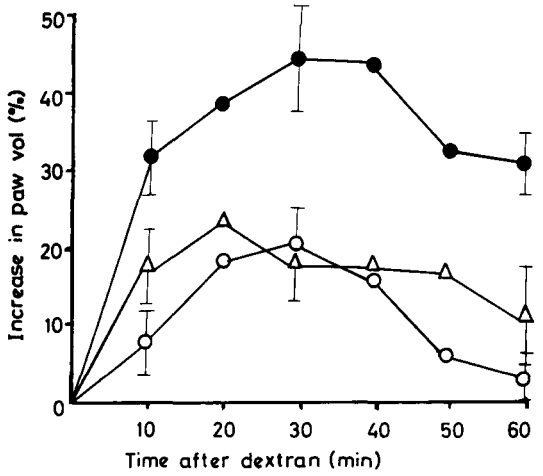

FIG. 2. Effect of dextran (50 μg, intraperitoneally) on the hind paw volume of R rats alone (○) and in the presence of sodium salicylate (● 30 μg and △ 15 μg). Again note the enhancement by sodium salicylate.

The enhancing action of sodium salicylate on the dextran response in R rats in some ways resembles that of insulin (Anderson et al 1978). With insulin, however, there is hypoglycaemia but this is not so with sodium salicylate. A direct effect of insulin on intact mast cells has recently been considered (West 1981) and so sodium salicylate may be exerting a similar effect on cell membranes. Aspirin in comparable doses failed to enhance the dextran reaction systemically or locally, and it is known that the rate of absorption of sodium salicylate is faster than that of aspirin (Martindale 1977). Furthermore, the dose of sodium salicylate used for enhancement of the dextran reaction in R rats did not enhance the local oedema reactions produced by histamine or 5 hydroxytryptamine. Finally, on isolated peritoneal mast cells of the R rats, sodium salicylate was not an enhancer when histamine release induced by dextran and phosphatidyl serine was measured.

A possible difference between sodium salicylate and aspirin relates to their effects on prostaglandin synthetase at different sites (Whittle et al 1980). For example, the levels of prostacyclin, the predominant cyclo-oxygenase product in the gastric mucosa, remain unchanged after sodium salicylate treatment whereas aspirin grossly depresses the levels. Being a potent mucosal vasodilator, prostacyclin may be involved in the local regulation of the gastric microcirculation, so removal of such tone after inhibition of endogenous prostacyclin biosynthesis by aspirin and indomethacin leads to areas of local ischaemia within the gastric mucosa, making them susceptible to attack by acid or pepsin with subsequent tissue necrosis and erosion. Sodium salicylate does not alter prostacyclin levels and has a protective action. A similar type of differentiation could well explain why sodium salicylate, but not aspirin or indomethacin, enhances the dextran reaction in R rats.

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