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Adrenocortical stimulation and the anti-inflammatory actions of salicylates

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The mechanism by which salicylates (and other acidic non-steroidal anti-inflammatory drugs) exert their anti-inflammatory activity has been a matter of some controversy for a number of years. Evidence accumulated over the last decade has led to a hypothesis that their mode of action resides in the ability of the drugs to inhibit the production of biologically active lipids from arachidonic acid by inhibiting prostaglandin cyclo-oxygenase (Ferreira & Vane 1979; Vane 1978). Whilst this effect is not disputed, there is now available a substantial literature which would argue that other anti-inflammatory actions of these drugs, particularly those directed against leucocyte accumulation in inflammatory exudates, are unrelated to their effects on prostaglandin cyclo-oxygenase (Walker et al 1976; Glenn et al 1977; Atkinson & Leach 1978; Smith 1978).

It is therefore pertinent to examine other actions of these drugs which may account for their effects on leucocyte accumulation at inflammatory sites. One possibility is stimulation of the adrenal cortex, a suggestion which originally arose because of the efficacy of steroids in rheumatic diseases (Hench 1950). While the evidence for this postulate, at least for anti-inflammatory doses of aspirin, is weak (Smith 1966), it has nevertheless recently been proposed that leucocyte accumulation into pleural exudates may be inhibited by a systemic action of aspirin via stimulation of the adrenal cortex (Vinegar et al 1978).

The experiments reported here were designed to explore the possibility that the inhibitory effects of aspirin, and its immediate metabolite, salicylic acid, on leucocyte accumulation and prostaglandin-like activity in subdermally implanted sponge exudates may be due to stimulation of the adrenal cortex.

The sponge implantation method, determination of prostaglandin-like activity and leucocyte accumulation in 9 h sponge exudates have been described in detail elsewhere (Ford-Hutchinson et al 1978). Bilateral adrenalectomy was performed by standard methods, the animals being maintained on 0·9% NaCl and used 8 days after the operation. Aspirin (acetylsalicylic acid) and salicylic acid (BDH, Poole, Dorset) were given orally as a suspension in Tween 80, or locally, distributed in the solid form throughout dry sponges (Walker et al 1976).

The results obtained after systemic administration of the drugs to normal and bilaterally adrenalectomized animals are shown in Tables 1 and 2. It is clear that bilateral adrenalectomy enhances two important aspects of the inflammatory reaction, the formation of prostaglandin-like activity, which has been increased approximately sixfold, and leucocyte accumulation in the exudate, which has doubled. The results of other experiments showed that sham-operated animals did not differ significantly from normal rats with respect both to the content of prostaglandin-like activity and leucocyte accumulation in the exudates and the effects of aspirin on these parameters. While the absolute values for both parameters are higher after treatment with either aspirin or salicylic acid in the adrenalectomized animals compared with the control groups, the mean percentage inhibition afforded by the drugs at the doses used are similar. Local application of aspirin and salicylic acid gave a predictable result; aspirin (0·5 mg) inhibited the production of prostaglandin-like material by 84% without affecting leucocyte accumulation (number of rats = 10), and salicylic acid (0·5 mg)

Table 1. Effects of oral administration of aspirin and salicylic acid on the accumulation of prostaglandin-like activity and leucocytes in 9 h sponge exudates in normal rats.

Drug	Dose mg kg^{-1}	PGE_2 equiv. (ng ml^{-1} exudate)	% inhibition	Total white cells ($\times 10^6$ ml^{-1} exudate)	% inhibition
Control (10)	—	10·3 ± 1·3	—	7·67 ± 0·50	—
Aspirin (5)	50	4·1 ± 0·1	59·8*	5·27 ± 0·35	31·3*
Aspirin (10)	200	2·1 ± 0·2	80·1*	3·93 ± 0·41	49·3*
Salicylic acid (5)	50	2·6 ± 0·3	75·2*	5·65 ± 0·25	26·0†
Salicylic acid (5)	200	2·0 ± 0·3	81·0*	4·39 ± 0·35	42·7*

Figures in parenthesis indicate the number of animals per group. Results expressed as mean ± s.e.m.
† $P < 0·05$, * $P < 0·005$.

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Table 2. Effects of oral administration of aspirin and salicylic acid on the accumulation of prostaglandin-like activity and leucocytes in 9 h sponge exudates in bilaterally adrenalectomized rats.

Drug	Dose (mg kg^{-1})	$PGE_{2\alpha}$ (ng ml^{-1} exudate)	% inhibition	Total white cells ($\times 10^6$ ml^{-1} exudate	% inhibition
Control	—	60·7 ± 7·0	—	12·89 ± 1·20	—
Aspirin	50	18·3 ± 5·6	69·8*	10·04 ± 1·27	22·1
Aspirin	200	9·8 ± 2·2	83·9*	6·43 ± 1·14	50·1†
Salicylic acid	50	22·5 ± 2·8	62·9*	10·58 ± 0·59	17·9
Salicylic acid	200	9·7 ± 1·3	84·0*	7·17 ± 1·14	44·4†

6 animals per group. Results expressed as mean ± s.e.m.
† $P < 0.01$, * < 0.001.

affected neither parameter significantly (number of rats = 6). These results provide strong evidence for a systemic action of these drugs towards inhibition of leucocyte accumulation thus supporting the findings of Vinegar et al (1978). The inhibition of prostaglandin-like activity by locally applied aspirin and salicylic acid when given systemically have been discussed elsewhere (Walker et al 1976; Smith 1978; Smith et al 1979 submitted for publication).

The enhancement of the inflammatory reaction in bilaterally adrenalectomized animals supports the concept that endogenous steroids control such responses. Hydrocortisone has been found to suppress the accumulation of both leucocytes and prostaglandin-like activity in sponge exudates in normal animals (Ford-Hutchinson et al 1978) although the inhibiton of prostaglandin production by this steroid has not been confirmed in a similar model of inflammation (Higgs et al 1976). Anti-inflammatory steroids have, however, been shown to inhibit prostaglandin release in vitro by several groups, probably by inhibiting membrane bound phospholipase A_2 activity (Blackwell et al 1978). The inhibition of leucocyte accumulation in sponge exudates (Ford-Hutchinson et al 1978) and the carrageenan paw oedema by steroids (Higgs et al 1976) may reflect the ability of steroids to reduce the adherence and movement of leucocytes, demonstrated in vitro using nylon fibres (MacGregor 1977) and Boyden chambers (Ward 1971).

The results obtained with systemic aspirin and salicylate in normal and bilaterally adrenalectomized animals do not support the view that their mechanism of action is via stimulation of the adrenal cortex. These findings uphold the conclusions drawn by Smith (1966) and Collier (1969) that stimulation of the adrenal cortex only occurs at drugs concentrations exceeding those required for the expression of anti-inflammatory activity.

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