EFFECT OF SALICYLATES ON VASCULAR RESPONSES

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Strom and Coffman (1) found that aspirin produced a significant reduction in peripheral blood flow responses to i.v. epinephrine and nor-epinephrine in human beings. Hashimoto *et al.* (2) studied the effect of sodium salicylate on reflex vascular responses to dimethylamino prophy-tetrahydro-azaazepino phenothiazine (RPP201), andromedotoxin, veratridine, bradykinin and kallikrein injected in the femoral or renal artery of the isolated hindlimb or kidney preparation perfused by cross-circulation. Sodium salicylate abolished completely the pressor response to RPP201, andromedotoxin, veratridine, bradykinin or kallikrein. The depressor response to the last two agents was, however, unaffected. Anticholinergic, antiadrenergic, antihistaminic, antiserotonin and neuromuscular or ganglion-blocking agents did not influence the reflex vascular response. Since salicylates are used as anti-inflammatory and anti-rheumatic agents, an action on the blood vessels may be of significance in the mechanism of this effect. Hence it was thought of interest to study the effect of salicylates on responses to certain other pressor and depressor agents. The results obtained are reported in this communication. A preliminary report of the work has been presented [Ahmad and Dhawan (3)].

METHODS

The experiments were performed on healthy adult mongrel dogs of either sex anaesthetised with pentobarbital sodium (30 mg/kg/i.v.). The blood pressure was recorded from a cannulated femoral artery on a smoked kymograph paper by means of a mercury manometer. Drugs were administered via an indwelling polyethylene catheter in the femoral vein. Pressor responses were obtained by i.v. administration of epinephrine hydrochloride (10 μ g), nor-epinephrine tartrate (10 μ g) or ephedrine sulphate (10 mg), while depressor responses were obtained with acetylcholine chloride (250 μ g), papaverine hydrochloride (5 mg) or sodium nitrite (10 mg) administered by the same route. At least three responses to an agent were obtained during each experiment except in the case of ephedrine (where it was not possible due to tachyphylaxis) and sodium nitrite (where it was not possible due to prolonged effect). When the responses to all the agents had been obtained the vessels and the wound were closed aseptically and the animal allowed to recover. The animal was anaesthetised again two days later and similar responses were recorded from the femoral artery of the other side. Each animal thus served as its own control. In the intervening period the animal received 4 doses of sodium salicylate (250 mg/kg/i.m.). A group of five dogs served as a saline control, and received only an equal

volume of normal saline instead of sodium salicylate solution to obviate any effects due to the fluid administered or surgery. A group of twelve dogs was treated with sodium salicylate.

RESULTS

The results obtained in the salicylate and saline treated animals are summarized in Tables 1 and 2 respectively. The tables are identically constructed and show the mean, initial as well as the post-treatment response to each agent along with the standard error of mean. The significance of difference between the control and post-treatment responses was estimated by the Student's T test at 95% level ($P=0.05$). As is evident from Table 2, saline treatment did not significantly alter the response to any of the agents tested. Sodium salicylate, however, reduced the pressor response to ephedrine significantly (from 68 mm to 38 mm) while that to epinephrine or nor-epinephrine was not significantly affected. The depressor response to acetylcholine was on the contrary significantly increased (from 30 mm to 44 mm), the response to papaverine and sodium nitrite remaining unchanged (*see* Table 1).

The effect of sodium salicylate treatment on responses of ephedrine and acetylcholine is shown in Fig. 1. This figure shows the control response to each of these agents in two dogs one of which subsequently received sodium salicylate (No. 9) while the other (No. 14) received saline. As is evident in the figure the pre- and post-treatment responses

TABLE 1. Showing the effect of salicylate treatment on responses to certain pressor and depressor agents. The values marked with an asterisk (*) differ significantly ($P=0.05$) from the control values. For details see text.

Agent with dose	Control Response mmHg $\pm$ S.E.	Salicylate treatment Response mmHg $\pm$ S.E.
Epinephrine 10 μ g	40.0 $\pm$ 3.2	38.0 $\pm$ 8.0
Nor-epinephrine 10 μ g	50.0 $\pm$ 7.4	58.0 $\pm$ 7.2
Ephedrine 10 mg	68.0 $\pm$ 8.0	38.0 $\pm$ 8.0*
Acetylcholine 250 μ g	30.0 $\pm$ 2.0	44.0 $\pm$ 3.2*
Papaverine 5 mg	24.0 $\pm$ 4.0	22.0 $\pm$ 6.8
Sodium nitrite 10 mg	16.0 $\pm$ 3.2	16.0 $\pm$ 2.0

TABLE 2. Showing the effect of saline treatment on responses to certain pressor and depressor agents. For details see text.

Agent with dose	Control Response mmHg $\pm$ S.E.	Saline treatment Response mmHg $\pm$ S.E.
Epinephrine 10 μ g	32.0 $\pm$ 6.0	26.0 $\pm$ 4.0
Nor-epinephrine 10 μ g	44.0 $\pm$ 9.0	38.0 $\pm$ 3.0
Ephedrine 10 mg	66.0 $\pm$ 2.0	66.0 $\pm$ 2.0
Acetylcholine 250 μ g	22.0 $\pm$ 6.0	26.0 $\pm$ 6.0
Papaverine 5 mg	20.0 $\pm$ 2.0	20.0 $\pm$ 2.0
Sodium nitrite 10 mg	14.0 $\pm$ 6.0	10.0 $\pm$ 6.0

FIG. 1. The effect of salicylate (Dog 9) or saline (Dog 17) treatment on the blood pressure responses to ephedrine (upper panels) and acetylcholine (lower panels) in pentobarbitalised dogs. The upper tracing shows the femoral blood pressure and the lower tracing indicates the places where drugs have been administered i.v. Time between panel 1 and 2 is two days in each case. For further details see text.

are identical in the saline treated animal (98 and 100 in the case of ephedrine and 47 and 48 in the case of acetylcholine, respectively). In the salicylate treated animal the response to ephedrine fell from 110 mm to 30 mm while the response to acetylcholine increased from 30 mm to 55 mm (*see* Fig. 1). The saline or salicylate treatment did not produce any significant change in the blood pressure level (*see* Fig. 1).

DISCUSSION

There is no significant difference in the pre- and post-treatment response to any of the agents in the saline group. It is, therefore, clear that surgery or fluid administered have not modified in any way the responses to these agents. This is further supported by the fact that the response to a number of agents has not been modified by the salicylate treatment either (*see* Table 1).

The results obtained with epinephrine and nor-epinephrine do not agree with the findings of Strom and Coffman (*loc. cit.*). This may be due to species variation. Alter-

natively, as Strom and Coffman have studied responses of forelimb vessels only, salicylates may be having a specific effect on certain vascular beds which may not be reflected by responses of the blood pressure in the present study. This, however, appears unlikely since responses to ephedrine and acetylcholine have been modified (*see* Fig. 1). To further elucidate this, however, effect of salicylates on the responses of these agents on different vascular beds is being investigated and shall be reported later.

It is difficult to explain the mechanism by which salicylates modify the responses to ephedrine and acetylcholine in the present studies and to several other agents in the experiments of Hashimoto *et al.* (*loc. cit.*). Theoretically, the salicylates can produce this effect by (a) acting on the C.N.S. or the neural pathways from C.N.S. to the blood vessels (b) an action on the myocardium, (c) an action on the smooth muscles of the blood vessels or (d) modification of the metabolism of these agents. An action on the C.N.S. or the neural pathways is eliminated since several groups of drugs blocking the neural pathways failed to modify the effects of salicylates in the experiments of Hashimoto and co-workers (*loc. cit.*). An action on the myocardium also seems unlikely, as this ought to have modified the response to all the agents or at least to the agents having an action on the myocardium, e.g., epinephrine and nor-epinephrine. A direct effect on the smooth muscles of the blood vessels can be ruled out by the fact that the response to directly acting agents like papaverine or nitrites has not been modified. Salicylates may, therefore, be possibly modifying the metabolism of these agents in the body and thus altering their vascular responses. This contention is also supported by the fact that the salicylates are known to have multiple effects on metabolic processes and cellular metabolism [Goodman and Gilman (4) and Smith (5)].

SUMMARY

1. The effect of sodium salicylate on blood pressure responses to acetylcholine, epinephrine, nor-epinephrine, papaverine and sodium nitrite in pentobarbitalised dogs has been investigated.
2. Sodium salicylate significantly reduces the pressor response to ephedrine while the depressor response to acetylcholine is significantly increased.
3. The findings are discussed in the light of reports available in the literature.

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