A NOTE ON
SODIUM SALICYLATE AND TISSUE 5-HYDROXYTRYPTAMINE IN THE RAT

BY M. MEDAKOVIĆ AND B. RADMANOVIĆ

From the Department of Pharmacology, Medical Faculty of Belgrade, Yugoslavia

Received June 7, 1960

The treatment of rats with large doses of sodium salicylate induces a marked decrease in the 5-hydroxytryptamine level of the skin without depleting the stores in the ileum.
After the addition of sodium salicylate to rat incubated skin, an increased release of 5-hydroxytryptamine into the surrounding fluid was noted in only 3 instances out of 10 using Vane's preparation of the rat fundus for the assay.

THE subcutaneous injection of very small doses of 5-hydroxytryptamine (5-HT) causes a local inflammatory response in the rat[1]. The generalised[2], as well as the local[3] egg white anaphylactoid inflammatory reaction in rats is intimately connected with the release of 5-HT. The pretreatment of the rats by substances which release 5-HT, such as 48/80 or reserpine can mitigate or prevent the generalised[2] and local egg white reaction[3].

Sodium salicylate antagonises the inflammatory action of 5-HT[4] and has been shown to inhibit *in vitro* the anaphylactic release of histamine

TABLE I

THE INFLUENCE OF SODIUM SALICYLATE (1·5 G./KG. WEIGHT FOR 4 DAYS, I.P.) UPON THE CONTENT OF 5-HT IN THE RAT SKIN AND ILEUM

	5-HT μg./g. tissue ± S.E. of the mean	
	Controls	Sodium salicylate treated animals
Skin	1·087 ± 0·161	0·504 ± 0·112 P <0·01
Ileum	1·020 ± 0·210	1·100 ± 0·190

from the guinea pig lung[5,6] and from the rabbit blood[7]. As body 5-HT often has a fate similar to that of body histamine, we have studied the influence of sodium salicylate treatment upon the 5-HT stored in the rat skin and intestine.

METHODS

White rats of both sexes were treated with daily sodium salicyclate by intraperitoneal injection (1·5 g./kg.) for four days. On the fifth day the animals were killed. The abdominal skin was shaved, cut into small pieces and extracted for 5-HT by the method of Coreale[8]. A piece of ileum was washed and also extracted. Control animals were injected with saline for four days. The samples of tissue extracts were tested for their 5-HT activity on Vane's[9] rat fundus preparation.

The *in vitro* experiments were done with the rat skin. A part of the abdominal skin was shaved, cut into small pieces and put into Krebs'

solution (1 g. of the skin in 10 ml. at 37°). This solution was then tested for its 5-HT activity before and after the addition a given dose of sodium salicylate. A small volume (0·1–0·2 ml.) of this fluid was added to a bath (10 ml.) with the isolated rat fundus preparation. For this preparation Krebs solution (at 37°) containing 10^{-7} atropine and 10^{-6} antazoline was used.

Results

As shown in Table I, the treatment with sodium salicylate lowered the 5-HT content of the rat skin. The quantity found in the skin after four days of treatment with 1·5 g./kg. salicylate daily amounted to only one half of the normal value. The difference was significant at the 1 per cent level of probability ($P<0·01$). In contrast to the skin, the quantity of 5-HT in the rat ileum was not lowered by sodium salicylate treatment but seemed to be slightly increased. However, the difference from the control value was not significant.

The *in vitro* experiments showed that the addition of sodium salicylate caused an increased in the activity of the incubation fluid in only three out of ten experiments. The addition of sodium salicylate to the bath with the Vane's preparation did not change its responsiveness when the drug was added in concentrations up to 10^{-5} g./ml. The same concentrations did not contract the test preparation. Hence, it seems feasible to assume that the increase of the activity of the incubation fluid, which was obtained after the addition of sodium salicylate, was caused by an increase in the concentration of the active substance in this fluid. As the bath fluid of the test preparation contained atropine and antazoline and as the effect of the incubation fluid was abolished by bromolysergic acid diethylamide it is thought that the active substance was 5-HT. This result would mean that the addition of sodium salicylate caused an increased release of 5-HT from the rat skin, which is in accordance with the *in vivo* experiments. The fact that the increase of 5-HT activity of the incubation fluid occurred in only 3 out of 10 experiments may be explained by assuming that minute quantities of 5-HT were released initially by the skin, so that the test preparation could not register the differences of the activity induced by sodium salicylate.

It should be mentioned that sodium salicylate when present in the bath with the Vane's rat fundus preparation in concentrations higher than 10^{-5}, reduced or inhibited both 5-HT and incubation fluid effects.

Discussion

The present experiments have shown that the treatment with sodium salicylate increased the release of 5-HT from the stores in the rat skin. It is interesting that only the skin 5-HT level was so lowered; the 5-HT content of the intestine not being significantly changed. The cause of this difference in the susceptibility of 5-HT stores in these two preparations to the action of sodium salicylate is not known. However, similar findings were described for reserpine[2] and cortisone[10]. Both these drugs more readily influenced the 5-HT stores in the skin than in the intestine.

It has been shown that sodium salicylate lowers the permeability of the subcutaneous tissue in the rat[4] and in the rabbit[12], acting unspecifically through the adrenal hormones. As variations in tissue 5-HT store might be expected to influence the tissue permeability, the present experiments suggest that the influence of sodium salicylate upon the tissue permeability may be related with its action upon the level of 5-HT in store. Therefore, the anti-inflammatory action of sodium salicylate may be related to its action on tissue 5-HT or other inflammatory substance(s) stored in various tissues or both. It might be expected that the tissue, depleted of humoral inflammatory agent by treatment with sodium salicylate, would react less readily to various factors which are thought to produce the inflammation by releasing such tissue agents from their stores.

It is interesting to note that 5-HT, itself injected in very high doses, had an anti-inflammatory action in the rat[3]. However, this action of 5-HT was probably mediated through a modification of the hormonal secretion of the adrenals[14].

References

1. Rowley and Beneditt, *J. exp. Med.*, 1955, **103**, 399.
2. Parratt and West, *J. Physiol.*, 1957, **139**, 27.
3. Medaković, *Arch. int. Physiol. Biochim.*, 1959, **67**, 2.
4. Kelemen, *Brit. J. Pharmacol.*, 1957, **12**, 26.
5. Trethewie, *Austr. J. exp. Biol. med. Sci.*, 1951, **29**, 443.
6. Ungar and Damgaard, *J. exp. Biol.*, 1955, **101**, 1.
7. Haining, *Brit. J. Pharmacol.*, 1956, **11**, 357.
8. Coreale, *J. Neurochem.*, 1958, **2**, 201.
9. Vane, *Brit. J. Pharmacol.*, 1957, **12**, 344.
10. Hicks and West, *Nature, Lond.*, 1958, **181**, 1342.
11. Kelemen, Majoros, Ivanyi and Kovacs, *Experientia*, 1950, **6**, 435.
12. Jacot, Ducommun, Timiras and Selye, *J. Physiol.*, 1951, **43**, 621.
13. Georges and Herold, *C.R.Soc. biol., Paris*, 1957, **151**, 692.
14. Georges, *ibid.*, 1957, **151**, 695.