Antihistamine constriction in mouse skin microcirculation

SIR,—Evidence has recently accrued, using direct *in vivo* microscopy of various regional circulations, that some structurally unrelated antihistimines, e.g., ethanolamines (diphenhydramine), ethylenediamines (pyrilamine), phenothazines (promethazine) and dimethylpropylamines (chlorpheniramine), have a dose dependent constrictor action on the muscular micro-vessels of mesenteries and omentums of rats, rabbits and guinea-pigs which resembles the profile of vascular reactivity for adrenaline and noradrenaline in the microcirculation (Altura, 1964; Altura & Zweifach, 1965a, Haley & Harris, 1949; Haley & Andem, 1950). Further, these various antihistamines sensitized various muscular micro-vessels (precapillaries, metarterioles, arterioles, venules, small arteries, small veins) to the constrictor actions of adrenaline and noradrenaline and *vice-versa* (Altura & Zweifach, 1964, 1965a). In addition, we have shown that the contractions induced by these antihistamines cannot be ascribed to circulating noradrenaline, adrenaline or 5-hydroxytryptamine (5-HT) and are

TABLE 1. EFFECTS OF TOPICAL APPLICATION OF ANTIHISTAMINES ON MICRO-VESSELS IN MOUSE SKIN MICROVASCULATURE. Antihistamines applied to surface of exposed skin microvasculature in volumes of 0·05 ml. Symbols (+) represent degree of microvascular constriction (+ = 10–15% decrease in vessel diameter size). Groups of 5 animals were used for each dose

Antihistamine (dose in μg)		Precapillary sphincter	Arteriole	Venule
Chlorpheniramine maleate	0·1	++	+	0
	1·0	+++	++	0
	10·0	++++*	+++	0
	15·0	++++*	++++*	++**
Diphenhydramine hydrochloride	0·5	++	+	0
	5·0	+++	++	0

*++++—Represents complete closure of these vessels.
** Represents stasis, petechial formations and leucocytic sticking at these vessel sites in addition to the contractile response.

not dependent upon anticholinergic or local anaesthetic actions (Altura & Zweifach, 1965b). We have also shown that these antihistamines cannot be exerting their microvascular effects through a release of catecholamines from peripheral sympathetic stores on to the vascular smooth muscle effector unit, which may be inaccessible to adrenergic blocking agents (Altura & Zweifach, 1966).

In view of the implications of these findings, it has been thought advisable to determine the effects of some of these antihistamines on the skin microvasculature.

Male C57 BL/6J mice, weighing 20–25 g, were anaesthetized with pentobarbitone sodium, 6 mg/100 g body wt intramuscularly. Hair on the dorsal surface was shaved and depilated. A transparent lucite skin chamber was then implanted in each mouse (Zarem, Zweifach & McGehee, 1967), areolar tissue removed, and the exposed blood vessels of panniculus carnosus and skin observed. One dose of each antihistamine (made up fresh daily in isotonic saline) was then topically applied, in 0·05 ml amounts to the exposed vascular tissue of the skin chamber preparation and examined at a magnification of 65–500 × with a Leitz Ortholux microscope equipped with Ultropak lenses. The results are shown in Table 1.

Both chlorpheniramine maleate and diphenhydramine hydrochloride exerted a dose-dependent constrictor action on the skin micro-vessels, which progressed from precapillaries to arterioles to venules in terms of vessel sensitivity.

Isotonic saline (vehicle), on the other hand, exerted no vascular effects. The doses, of antihistamines, which elicited threshold precapillary contractile responses were extremely low (0·1–1·0 μg), while arteriolar-venular (A–V) shunts seemed to remain unaffected until much higher doses were applied (10–15 μg). However, these latter high antihistamine doses, approximately 100–150 × threshold, also produced irreversible microvascular injury in most of the preparations tested, in the form of postcapillary venular stasis, petechial formations and sticking of leucocytes to endothelial walls. The microcirculatory actions of the antihistamines (0·1 to 5·0 μg) lasted for protracted periods (3 to 60 min) depending on the dose; the lower the dose the shorter was the duration of constrictor action.

These experiments suggest that certain antihistamines–chlorpheniramine maleate and diphenhydramine hydrochloride, among others—may exert anti-inflammatory actions, in very low doses, at least in mouse skin microcirculation, by virtue of their ability to induce direct microvascular contractile responses possibly similar in action to the effects of the local anti-inflammatory hormones-adrenaline and noradrenaline (Willoughby & Spector, 1964). The actions of the antihistamines on the small blood vessels of the skin, like the catecholamines, result primarily in precapillary vasoconstriction (i.e., no flow into true capillaries) and would inhibit the increased capillary permeability seen in certain local inflammatory conditions, thus preventing the escape of intravascular fluids and other plasma constituents into the perivascular connective tissue. As shown by Landis (1927), vasoconstriction (closure) of metarterioles and precapillaries induces a return of extravascular fluid and other plasma constituents from the extravascular compartment into the true capillary circulation as originally suggested by Starling. In this context, Spector & Willoughby (1963), among many others found that various antihistamines inhibited a variety of permeability inducing factors, in addition to histamine, in rat skin, as measured by the trypan blue dye labelling technique.

These results on small blood vessels in mouse skin may help to explain why antihistamines are effective in ointments as anti-inflammatory agents.

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