Bradykinin antagonism by dimethothiazine

Dimethothiazine [10-(2-dimethylaminopropyl)-2-dimethylsulphamoylphenothiazine] is now in clinical use as an antihistamine-anti-5-hydroxytryptamine agent. Joulou, Ducrot & others (1966) reported that it had fifteen times the activity of aspirin against pain induced by intraperitoneal injection of bradykinin in mice but there appear to be no other studies of this effect. We have compared the bradykinin antagonism of dimethothiazine with that of cyproheptadine (Garcia Lemme & Rocha e Silva, 1965) in several preparations.

The central vein of the rabbit ear perfused by the method of de la Lande & Rand (1965) is exceptionally sensitive to kinins but responds to few other substances (Mashford & Horowitz, 1968). On this preparation both dimethothiazine and cyproheptadine showed moderate antagonism to the effects of bradykinin (Fig. 1). The concentration of dimethothiazine necessary to produce a definite effect was usually 10 μg/ml (Fig. 1a). The non-competitive nature of this antagonism became evident at higher concentrations where there was a distinct reduction of the slope of the dose-response plot. A similar situation pertained with cyproheptadine (Fig. 1b). Since the rabbit ear vein responds to few agonists other than kinins, the specificity of the antagonism could not be tested, but bradykinin antagonism was also demonstrated

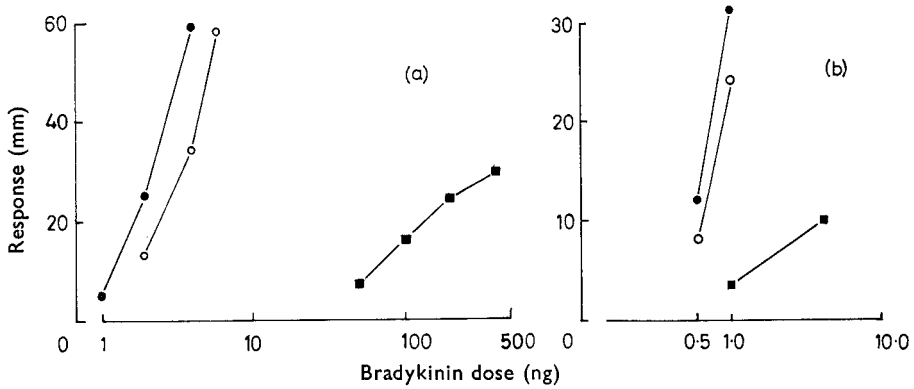

FIG. 1. Dose-response curves of rabbit isolated ear vein to bradykinin. a. Effect of dimethothiazine. b. Effect of cyproheptadine. ●——● control. ○——○ 10 μg/ml of drug. ■——■ 50 μg/ml of drug in a and 100 μg/ml of drug in b.

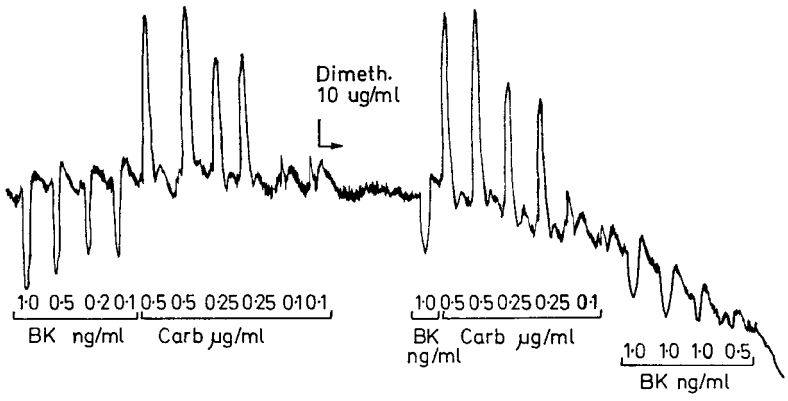

FIG. 2. Responses of superfused duodenum to bradykinin (BK) and carbachol (Carb). Addition of 1·0 μg/ml dimethothiazine to the superfusion fluid caused a relaxation and impaired subsequent response to bradykinin. Carbachol responses were unaltered.

TABLE 1. *Antagonism of various agonists by dimethothiazine and cyproheptadine in some* in vitro *preparations*

Preparation	Agonist	Degree of antagonism: Dimethothiazine μg/ml			Cyproheptadine μg/ml		
		1	10	100	1	10	100
Rabbit ear vein	Bradykinin	0	+	++++	±	+	++
Rat uterus	Bradykinin	0	++	+++	0	++	+++
	Angiotensin	0	0	0	0	0	++
Rat colon	Bradykinin	+++	++++	—	+	+	—
	Angiotensin	0	0	±	0	0	—
Rat vas deferens	Bradykinin	+		++ (50 μg/ml)	— —	—	—
	Acetylcholine	0		0	—	—	—
Rat duodenum	Bradykinin	+++	++++	—	0	+	+
	Carbachol	0	0	—	—	—	—
	Noradrenaline	0	—	—	0	0	0

— = effect not tested.
0 = no antagonism.
+ = definite slight antagonism.
++ = approximate halving of response.
+++ = marked antagonism.
++++ = response abolished.

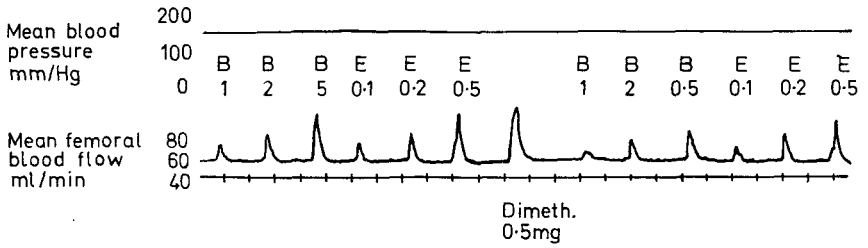

FIG. 3. Mean aortic blood pressure and mean femoral blood flow measured with an electromagnetic flowmeter in an anaesthetized dog. Injections of bradykinin (B) and eledoisin (E) into the femoral artery caused marked increase in femoral flow. Dimethothiazine 0·5 mg also increased flow but subsequent responses to bradykinin were much reduced; eledoisin responses were less effected.

with several other preparations. These were the rat uterus, duodenum, vas deferens and colon. Both the contractile effects as seen in the uterus, colon and vas deferens and the relaxation caused by bradykinin in the duodenum were antagonized by both agents. Although they are also potent antagonists to histamine and 5-HT there is some specificity since the responses of the various preparations to other agonists, such as angiotensin, carbachol, and acetylcholine, were not diminished by the presence of either compound in concentrations causing marked blockade of bradykinin responses (Table 1). Dimethothiazine appears to be a partial kinin-like agonist in the rat colon and duodenum as it caused contraction and relaxation (Fig. 2) respectively on its first application. Dimethothiazine also had a similar pattern relative to bradykinin in the dog femoral vascular bed, its injection causing a transient dilatation followed by a depression of responses to bradykinin (Fig. 3).

Dimethothiazine thus appears to act as a partial kinin-like agonist in a number of preparations and to produce a degree of non-competitive blockade in all tissues examined. At doses up to 10 μg/ml, the bradykinin antagonism was not due to non-specific depression of the preparations since response to angiotensin of uterus and colon, to carbachol of the duodenum, and to acetylcholine in the vas deferens were

unimpaired. Increasing the dose to 100 μg/ml often depressed responses to all agonists. The bradykinin-induced vasodilation in the dog femoral vascular bed and the relaxation of the rat duodenum were affected by dimethothiazine to the same extent as the contraction responses of the other varieties of smooth muscle studied. If the bradykinin blockade can be interpreted as some sort of interaction with kinin receptors, these observations provide no evidence of the sort of heterogeneity revealed by antagonists in the case of catecholamines.

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5-Hydroxyindole compounds in the perfusates from frog head

A series of investigations on the significance and role of 5-hydroxytryptamine (5-HT) have been made *in vitro*, in which the content of 5-HT and its metabolites in the brain of dead animals was measured. We have now made experiments with the perfused frog head, with the object of detecting whether there are in the perfusate any substances with properties of 5-hydroxyindoles (5-OH indoles) and also whether their content changes after administration of substances which interfere with biosynthesis, liberation or metabolism of 5-HT.

Male frogs (*Rana esculenta*, L.) were perfused as described by Trendelenburg (1938) with slight modifications: the perfusion fluid was administered through the truncus arteriosus and the collection of the perfusion fluid was via a polyethylene tube inserted in the sinus venosus. After a 1 h washing period, the specimens of perfusate were collected during the next 2 h. In these samples 5-OH indoles were estimated fluorimetrically (Ashcroft & Sharman, 1962). The following substances were used: 5-hydroxytryptophan (DL-5-hydroxytryptophan, Aldrich Chemical Co.), reserpine (Serpasil, Ciba), α-methyldopa (Aldomet, Merck), chlorpromazine (Largactil, Specia) and iproniazid (Marsilid, Roche). The doses of chlorpromazine and iproniazid are expressed as the free base, and the substances were administered subcutaneously.

In the perfusates of untreated animals we found substances with fluorescent properties of 5-OH indoles, the content of which was altered by administration of the above mentioned drugs. The results are summarized in Table 1. 5-Hydroxytryptophan induced a remarkable increase of the concentration of the total 5-OH indoles. After reserpine there was also a significant rise of 5-OH indole compounds in the perfusion fluid. α-Methyldopa lowered the content of total 5-OH indoles. Perfusion fluid from frogs pretreated with chlorpromazine showed an increased amount of 5-OH indoles. Samples from frogs treated with iproniazid showed no measurable fluorescence.

Our results with experiments *in vivo* obtained after administration of 5-hydroxytryptophan, reserpine and α-methyldopa are in good agreement with the results of related experiments *in vitro* (Udenfriend, Weissbach & Bogdanski, 1957; Pletscher,