THE MECHANISM OF THE LOCAL INFLAMMATORY REACTION INDUCED BY COMPOUND 48/80 AND DEXTRAN IN RATS

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The butanolamide of 1-methyl-lysergic acid (UML) and cyproheptadine are strong inhibitors of the local inflammatory reaction induced by 5-hydroxytryptamine (5-HT) in rats, but only cyproheptadine is active against histamine. As cyproheptadine is more active than UML in reducing the local oedema reaction induced by dextran and compound 48/80 in intact and adrenalectomised rats, it is suggested that both histamine and 5-HT are involved in the reaction.

THE local inflammatory reaction induced by compound 48/80 or dextran in rats is thought to be mediated by a release of 5-hydroxytryptamine (5-HT) and histamine (Engelhardt and Schwabe, 1960; Halpern, Liacopoulis and Liacoupoulos-Briot, 1959; Parratt and West, 1957; von Mörsdorf and Fehres, 1959; West, 1961). Exogenous 5-HT is many times more active than histamine in producing this reaction (Sparrow and Wilhelm, 1957; Spector and Willoughby, 1957; Ungar, Kobrin and Sezesny, 1959) and the problem needed further investigation.

Two recently-introduced drugs have been used: (i) UML, the butanolamide of 1-methyl-lysergic acid, a specific powerful anti-5-HT agent with few central actions (Berde, Doepfner and Cerletti, 1960; Doepfner and Cerletti, 1958; Hillebrecht, 1959) and (ii) cyproheptadine (1-methyl-4, 5-dibenzo[a,e]-cycloheptatrienylidene piperidine), a powerful anti-5-HT and antihistamine agent (Stone, Wenger, Ludden, Stavorski and Ross, 1961). Gelfand and West (1961) have recently shown that UML reduces the oedema reaction produced in rats by dextran and by compound 48/80 but is ineffective against histamine. The effect of these drugs on the local inflammatory reactions induced by 5-HT, histamine, dextran and compound 48/80 have therefore been studied in both intact and adrenalectomised rats.

EXPERIMENTAL

Methods

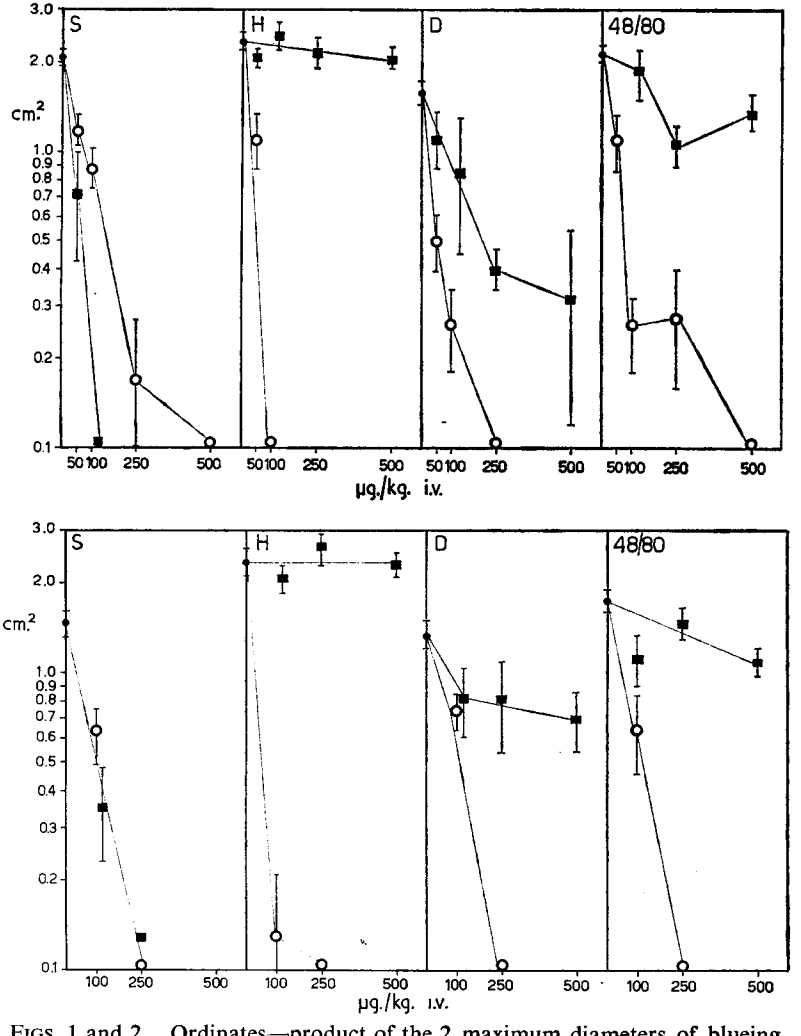
The abdominal skin of groups of female Sprague-Dawley rats (weighing about 150 g.) was depilated 24 hr. before the test. UML bimaleate (kindly supplied by Sandoz, Ltd., Milan) and cyproheptadine hydrochloride (kindly supplied by Merck, Sharp and Dohme, West Point, Pa.) were injected intravenously 30 min. before 2 mg. Evans Blue dye (0·4 per cent in water) and then four intradermal injections were made on each rat with 0·1 ml. each of 5-HT (2·5 μg./ml.), histamine (1 mg./ml.), dextran (1·2 mg./ml.) and compound 48/80 (10 μg./ml.). These doses produced similar degrees of blueing. The responses were evaluated by multiplying together the two maximum diameters of blueing 30 min. after the intradermal injections.

Control experiments were made to test the reaction arising from saline and that from the different sensitivities of the various areas of the abdominal skin.

Similar experiments were also made in rats which had been adrenalectomised 72 hr. previously and maintained on food and salt water. The doses of the oedema-producing agents were half those used in intact animals.

Results and Discussion

The results using intact rats are shown in Fig. 1. Small doses of UML prevent the oedema and blueing induced by 5-HT but have no anti-



FIGS. 1 and 2. Ordinates—product of the 2 maximum diameters of blueing (log scale). Abscissae—intravenous doses of cyproheptadine (○) or UML (■) given 30 min. before Evan's Blue dye.
The vertical bars represent the standard error of the mean.
Upper figure shows results obtained in unoperated rats;
lower figure in adrenalectomised rats.
S = Serotonin (5-HT) H = Histamine D = Dextran.

histaminic effect and only slightly reduce the effects after dextran or compound 48/80. Cyproheptadine is very active on both histamine and on 5-HT, although less active on 5-HT than is UML. Dextran and 48/80 induced oedema are more markedly decreased by cyproheptadine than by UML.

In Table I are shown the percentages of rats responding to the treatment. The results using adrenalectomised rats are plotted in Fig. 2 and are similar to those with intact animals, except that UML is slightly less active

TABLE I

THE EFFECT OF CYPROHEPTADINE AND UML ON THE BLUEING RESPONSE IN RATS INDUCED BY 5-HT, HISTAMINE, DEXTRAN AND COMPOUND 48/80

Treatment (μg./kg. i.v.)		Experimental condition	No. rats showing blueing/No. rats treated (and per cent) (controls = 100)			
			5-HT	Histamine	Dextran	48/80
Cyproheptadine	50	Intact rats	7/7 (100)	7/7 (100)	6/7 (85)	7/7 (100)
	100	"	9/10 (90)	3/10 (30)	5/10 (50)	8/10 (80)
	250	"	5/9 (55)	1/9 (11)	0/9 (0)	6/9 (66)
	500	"	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)
UML	50	"	3/4 (75)	4/4 (100)	4/4 (100)	4/4 (100)
	125	"	0/4 (0)	4/4 1(00)	3/4 (75)	4/4 (100)
	250	"	0/7 (0)	7/7 1(00)	4/7 (57)	7/7 1(00)
	500	"	0/7 (0)	7/7 1(00)	2/7 (28)	7/7 1(00)
	1000	"	0/4 (0)	4/4 (100)	0/4 (0)	4/4 (100)
Cyproheptadine	100	adrenalectomised	6/7 (85)	4/7 (57)	7/7 (100)	7/7 (100)
	250	"	3/4 (75)	0/4 (0)	3/4 (75)	2/4 (50)
	500	"	1/4 (25)	0/4 (0)	1/4 (25)	1/4 (25)
UML	125	"	3/4 (75)	4/4 (100)	4/4 (100)	4/4 (100)
	250	"	2/6 (33)	6/6 (100)	4/6 (66)	6/6 (100)
	500	"	2/9 (22)	9/9 (100)	9/9 (100)	9/9 (100)

against dextran and 5-HT. This suggests that the two drugs are chiefly acting directly on the oedema producing agents without interfering with adrenal function to any great extent. Since drugs with specific anti-histaminic effects only slightly reduce the dextran and 48/80 induced local oedema in rats (Halpern, Liacopoulos and Liacopoulos-Briot, 1959; Parratt and West, 1957) it is concluded that these are best explained on the basis of a participation of, at least, both mediators 5-HT and histamine.

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