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Effect of adrenergic drugs on histamine forming capacity of human leucocytes

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It has been shown (Assem, Schild & Vickers, 1972) that when isolated human leucocytes obtained from allergic subjects are incubated with specific antigen, they not only release histamine, but also exhibit a stimulation of their histamine forming capacity (HFC), as shown by an isotope dilution method. This effect has been shown both *in vitro* and *in vivo*. Since earlier work (Assem & Schild, 1969) had shown that anaphylactic histamine release is inhibited by isoprenaline, an effect which is antagonized by propranolol, we investigated whether drugs acting on α- and β-adrenoceptors would have a similar effect on HFC stimulated by antigen (*Dermatophagoides pteronyssinus*) in human leucocytes.

The results obtained (Table 1A) not only confirmed previous findings that antigen stimulates HFC (Assem *et al.*, 1972), but also showed that isoprenaline antagonized HFC stimulation by antigen, reducing the level of HFC below the control level in the absence of antigen. Propranolol, on the other hand, was found to potentiate HFC stimulation by antigen. In view of these findings, we decided to investigate

TABLE 1. *Effects of drugs on HFC (DPM±S.E.) in human leucocytes*

A. Drug effects on HFC stimulated by antigen
(Dermatophagoides pteronyssinus)

		Drug		Controls	
Exp. No.		M	Drug+Antigen	No Antigen	Antigen
I	Isoprenaline	10^{-4}	2·1±1	11·4±3	89±11
		10^{-5}	0·7±1	11·4±3	89±11
II		10^{-4}	71·5±3	126±4	184±18
III		4×10^{-5}	176±3	52·6±4	67·6±4
IV	Propranolol	10^{-4}	301±15	126±4·2	184±18
		10^{-5}	445±41	126±4·2	184±18
		10^{-6}	582±26	126±4·2	184±18
V		10^{-6}	885±18	481±20	664±11
		10^{-7}	605±15	481±20	664±11
		10^{-8}	512±48	481±20	664±11
VI		4×10^{-5}	325±10	52·6±4	64·6±3

B. Drug Effects on HFC without antigen

Exp. No		Drug M	Drug (No Antigen)	Controls (No Antigen)
I	Propanolol	10^{-5}	132±63	392±23
II		10^{-6}	617±33	481±20
III		10^{-6}	194±10	125±4
IV		10^{-6}	116±9	55·7±6
		10^{-7}	80·4±5	55·7±6
V	Phenylephrine	10^{-5}	181±14	125±4
VI		10^{-5}	147±16	91·1±13
		10^{-6}	120±4	91·1±13
VII	Phentolamine	10^{-5}	247±21	392±23

whether this effect on HFC by propranolol (and by other drugs acting on α- and β-adrenoceptors) could be obtained in the absence of antigen as well.

It was found (Table 1B) that propranolol greatly stimulated HFC in human leucocytes even in the absence of antigen, and in low concentrations (i.e. 10^{-7}M). Drugs acting on α-adrenoceptors appeared to produce effects opposite to those of drugs acting on β-adrenoceptors, phenylephrine stimulating HFC, and phentolamine inhibiting it. The possible significance of these results will be discussed.

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Hypersensitivity to adrenoceptor agents in the guinea-pig *in vitro* and *in vivo*

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Increased mortality in patients using bronchodilator sympathomimetic aerosols over extended periods (Speizer, Doll, Heaf & Strang, 1968) may be the result of hyposensitization to both endogenous and exogenous sympathetic stimulation as a consequence of excess usage of these sprays (Conolly, Davies, Dollery & George, 1971). Conolly *et al.* (1971) have described cardiovascular resistance to β-adrenoceptor stimulant drugs after prolonged exposure to these agents in man and dog, and increased histamine susceptibility (expressed as increased mortality after histamine administration) in the guinea-pig after similar treatment. We reproduced an analogous situation *in vitro* and repeated the *in vivo* mortality experiments in guinea-pigs.

Female guinea-pigs (Hartley strain ; 200–250 g) were used. Spirally cut tracheal strips (Constantine, 1965) were suspended in 10 ml organ baths containing Tyrode solution (containing 17 μg ascorbic acid/ml) at 38° C, aerated with 95% O_2 and 5% CO_2. Contractions were recorded isometrically on a pen recorder. In addition, several preparations were examined isotonically. Immediately after incubation with (−)-isoprenaline hydrochloride (50 ng/ml for 20 min) the contractile