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Antagonism of noradrenaline and histamine by desipramine in the isolated artery of the rabbit ear

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Summary

1. The effects of desipramine (DMI) were examined on the vasoconstrictor responses of the isolated perfused artery of the rabbit ear to noradrenaline (NA) and to histamine. Innervated and sympathetically denervated arteries were used.

2. In innervated arteries, DMI in concentrations of 1×10^{-8} to 1×10^{-7}M enhanced the responses to NA ; higher concentrations reduced the responses. In sympathetically denervated arteries, DMI caused only reduction of the responses to NA.

3. Responses to histamine were reduced by DMI in both innervated and denervated arteries. DMI was considerably more potent as an antagonist of histamine than of noradrenaline.

4. The reduction by DMI of the responses to NA and histamine in both innervated and denervated arteries was associated with a parallel shift to the right of the concentration-response curves of the agonist and a depression of the maximal response. These effects of DMI were reversible.

5. Analysis of the data by the method of Arunlakshana & Schild (1959) showed the following: the antagonism of the action of NA by DMI on denervated arteries fulfilled the requirements for competitive antagonism ; antagonism of the action of NA on innervated arteries was not competitive ; antagonism of the actions of histamine on innervated and denervated arteries was not competitive.

6. It is suggested that DMI antagonizes the action of NA and histamine on the perfused artery of the rabbit ear in two ways: (i) reversible specific antagonism which is competitive for NA and not competitive for histamine ; (ii) reversible non-specific antagonism which is non-competitive for both agonists.

Introduction

Desmethylimipramine (desipramine, DMI) and other tricyclic antidepressant drugs enhance the responses to sympathetic nerve stimulation and exogenous noradrenaline (NA) of peripheral tissues innervated by sympathetic nerves (Sigg, Soffer & Gyermek, 1963 ; Kaumann, Basso & Aramendía, 1965). It is generally accepted that these effects are due to inhibition of the uptake of NA by adrenergic nerves (Axelrod, Whitby & Hertting, 1961 ; Glowinski & Axelrod, 1964 ; Iversen, 1965).

Tricyclic antidepressant drugs may also reduce responses to sympathetic nerve

stimulation and to exogenous NA. These effects are more apparent with high concentrations of these drugs and have been most frequently reported for DMI. Thus, responses of isolated vascular preparations to NA are reduced by DMI (Hrdina & Garrattini, 1967 ; Turker & Khairallah, 1967 ; Scriabine, 1969 ; Hrdina & Ling, 1970).

The dual actions of DMI in enhancing and reducing responses to sympathetic nerve stimulation and exogenous NA, were demonstrated by Bassett, Cairncross, Hacket & Story (1969) in the isolated, perfused ear artery of the rabbit and by Glover & McCulloch (1970) on the pressor responses of the pithed rat preparation.

Clinical studies have shown that chronic administration of DMI or imipramine can produce hypotension (Klerman & Cole, 1965 ; Carlsson, 1966). This side effect could be a consequence of antagonism by the antidepressant drugs of the vasoconstrictor action of NA released by sympathetic nerves.

Hrdina & Ling (1970) studied the mechanism of the antagonism by DMI on the action of NA on the perfused isolated renal artery of the rat and concluded that it was not competitive. However, Turker & Khairallah (1967) had previously suggested that DMI competitively antagonized the action of NA on rabbit aortic strips.

The present experiments with the isolated perfused central ear artery of the rabbit were undertaken to investigate the nature of the inhibitory actions of DMI on the responses to NA and histamine. In order to obviate the complications of blockade of neuronal uptake by DMI, experiments were performed with chronically sympathectomized arteries as well as innervated arteries.

Methods

Segments of the central artery of the rabbit ear were double cannulated *in situ*, transferred to a 10 ml organ bath and perfused at a constant flow rate (6 ml/min) with Krebs-Henseleit solution containing disodium ethylenediamine tetraacetic acid (EDTA), 20 μg/ml. The perfusion technique was the same as that described by de la Lande, Cannell & Waterson (1966). The perfusion solution and the Krebs-Henseleit solution in the organ bath, which bathed the extraluminal surface of the artery, were not allowed to mix ; these were maintained at 37° C and gassed with 5% carbon dioxide in oxygen.

Perfusion pressure was measured with a Statham P23Db pressure transducer coupled to a potentiometric recorder, calibrated from 0 to 200 mmHg (1 mmHg= 133·3 Nm^{-2}). Constrictor responses to NA and histamine were obtained by adding these drugs to the solution in the organ bath (extraluminally) until no further increase in perfusion pressure occurred (2 to 3 min). Each dose of NA or histamine was washed out over a 4 min period. DMI was added to both the perfusion reservoir and the organ bath reservoir so that both the intraluminal and the extraluminal surfaces of the artery were exposed to the same concentration of the drug.

Log concentration-response curves to NA and histamine were established before and after the addition of DMI by the sequential addition of doses of the agonists to the organ bath. Regression lines were fitted to the linear portions of the curves by the method of least squares. The regression lines were tested for linearity, the paired lines were tested statistically for coincidence and parallelism, and the

potency ratios were calculated. Potency ratios greater than 1 indicate enhancement and potency ratios between 1 and 0 represent reduction of the responses. Except where otherwise noted, in any one artery preparation, only a single concentration of DMI was used.

Chronically denervated arteries were prepared by surgical removal of the superior cervical ganglia 10 to 14 days before the arteries were used. For the surgery, rabbits were premedicated intravenously with hyoscine-*N*-butyl bromide (Buscopan, Boehringer), 10 mg, and a light anaesthetic dose (20 to 25 mg/kg) of sodium pentobarbitone. Surgical anaesthesia was maintained with ether. Immediately after the operation, and on the 2 subsequent days the rabbits were given 0·25 g procaine penicillin and 0·25 g streptomycin sulphate (Penmycin, Evans Medical) by intramuscular injection.

The denervated arteries were dissected and perfused as described for the innervated arteries, but were tested for completeness of denervation by periarterial electrical stimulation delivered through concentric bipolar electrodes. The stimulus parameters were: square wave pulses of duration 0·5 msec, frequency 10 Hz, amplitude 20 V in trains of 10 seconds. Arteries failing to respond to stimulation were considered to be fully denervated.

The following drugs were used: (−)-noradrenaline bitartrate (Levophed, Winthrop) histamine acid phosphate (B.D.H.) and desmethylimipramine hydrochloride (DMI, Geigy). These drugs were freshly prepared in distilled water; the noradrenaline dilutions contained 25 μg/ml L-ascorbic acid and 25 μg/ml EDTA. The concentrations of noradrenaline are expressed in terms of the base and the concentrations of histamine refer to the acid phosphate.

Results

Effects of desipramine on the noradrenaline concentration-response relationship

Innervated arteries

The effects of DMI on the NA concentration-response relationship depended upon the concentration of DMI. With concentrations between 1×10^{-8}M and 3×10^{-7}M, DMI enhanced the NA responses, causing a shift to the left of the NA concentration-response curve. With concentrations of DMI between 3×10^{-7}M and 3×10^{-6}M, the responses to NA were reduced and the concentration-response curve was shifted to the right. In most experiments, the log concentration-response curves obtained in the presence of DMI did not depart significantly from parallelism with the control concentration-response curves ($P > 0{\cdot}05$). However, the reduction of the responses to NA by DMI was associated with a depression of the maximal vasoconstrictor response to NA as the concentration of DMI was increased. All of the effects of DMI on the NA concentration-response relationship were reversed by washing the arteries with drug-free Krebs-Henseleit solution, although with high concentrations of DMI (1×10^{-6}M and 3×10^{-6}M) up to 50 min of washing was required before the responses to NA were fully restored to control levels.

The NA potency ratios calculated from the displacement of the concentration-response curves are plotted as a function of the DMI concentration in Figure 1.

Denervated arteries

To determine if the enhancement of responses to NA produced by low concentrations of DMI was due to inhibition of the uptake of NA by sympathetic nerves, experiments were carried out with sympathetically denervated arteries. In these

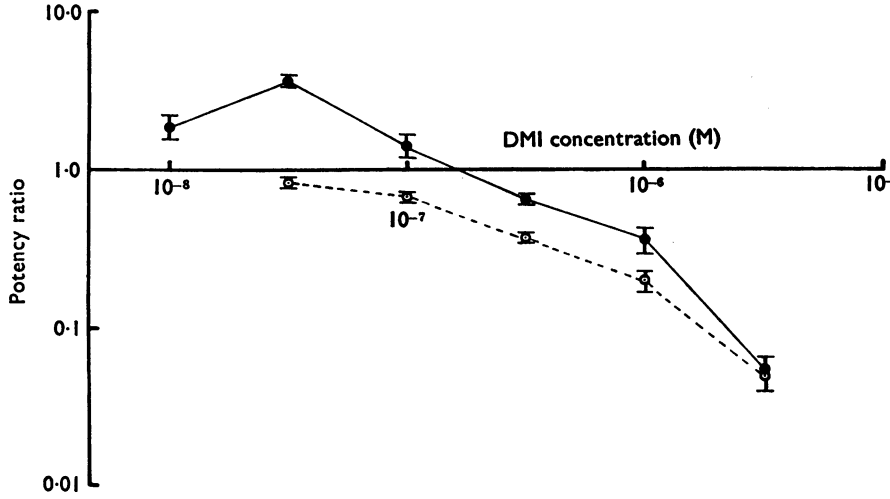

FIG. 1. Changes in responsiveness to noradrenaline (NA) produced by desipramine (DMI) in innervated arteries (●) and sympathetically denervated arteries (⊙). Potency ratios were calculated from the log concentration-response curves to NA. Values greater than 1 indicate potentiation of the action of noradrenaline and values less than 1 indicate antagonism. The symbols represent the means and the vertical bars the standard errors of the means of data from 2 to 6 artery preparations for each concentration of DMI. Ordinates: potency ratio (logarithmic scale). Abscissae: molar concentration of DMI (logarithmic scale).

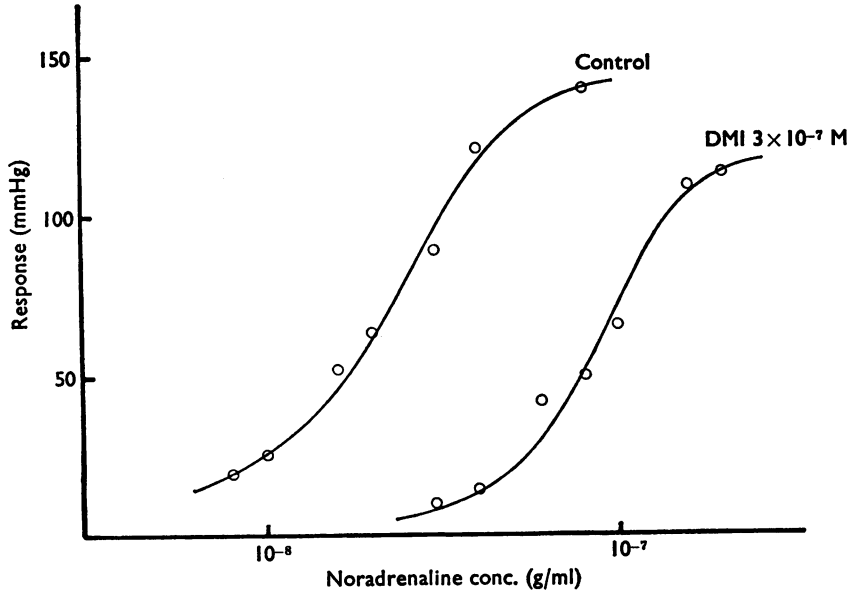

FIG. 2. The effect of 3×10^{-7}M desipramine (DMI) on the log concentration-response curve to noradrenaline (NA) in a denervated artery. Ordinates: response in mmHg (1 mmHg= 133·3 Nm^{-2}). Abscissae: concentration of NA (g/ml).

tissues, DMI in concentrations from 3×10^{-8}M to 3×10^{-6}M antagonized only the vasoconstrictor responses to NA (Fig. 1); a concentration of 1×10^{-8}M of DMI was without effect. As with the innervated arteries, the log concentration-response curves obtained in the presence of DMI did not depart significantly from parallelism with the control curves ($P>0.05$) and the maximal response was reduced, as illustrated in Fig. 2 with 3×10^{-7}M DMI. The effects of DMI on the concentration-response curves for NA in denervated arteries were reversed by washing.

The mean potency ratios obtained with all concentrations of DMI were compared with the results obtained for innervated arteries in Figure 1. With concentrations of up to 1×10^{-6}M, DMI produced a greater reduction of responses to NA in denervated arteries than in innervated arteries; however, with 3×10^{-6}M there was no significant difference between the mean potency ratios obtained on the two preparations ($P>0.05$).

Effects of desipramine on the histamine concentration-response relationship

Innervated arteries

The vasoconstrictor responses of innervated arteries to histamine were reduced by concentrations of DMI of 1×10^{-8}M and greater. The histamine log concentration-response curves were shifted to the right and remained parallel to the control curves ($P>0.05$). The maximal response to histamine was progressively reduced as the DMI concentration was increased. These effects, which are shown in Fig. 3, were reversed by washing the arteries in drug-free Krebs-Henseleit solution. The relationship between the concentration of DMI and the histamine potency ratio is illustrated in Figure 4. With all concentrations of DMI studied (1×10^{-8}M to 3×10^{-6}M) there was considerably greater reduction of the responses of the artery to histamine than to NA.

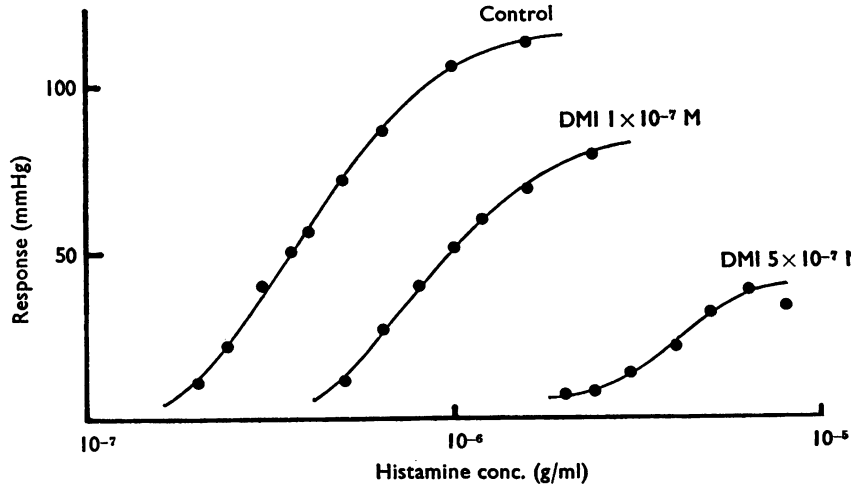

FIG. 3. The effect of desipramine (DMI) on the log concentration-response curve to histamine on an innervated artery. The 3 curves were obtained with a single preparation, the log concentration-response curve being established first in the absence and then successively in the presence of 1×10^{-7}M and 5×10^{-7}M concentrations of DMI. Ordinates: response in mmHg (1 mmHg=133·3 Nm^{-2}). Abscissae: concentration of histamine (g/ml).

Denervated arteries

As with innervated arteries, DMI produced only reduction of responses to histamine in denervated arteries. The potency ratios are shown in Figure 4. Concentrations of DMI from 5×10^{-8}M to 5×10^{-6}M caused a parallel shift ($P>0{\cdot}05$) of the log concentration-response curve to the right, and depressed the maximal response. With 1×10^{-7}M and 5×10^{-7}M there were no significant differences between the antagonism by DMI of the responses of innervated and denervated arteries to histamine (see Fig. 4). These effects were reversed by washing the tissue with drug-free solution.

Tests for competitive antagonism between desipramine and noradrenaline and desipramine and histamine

The findings that the log concentration-response curves to NA and histamine remained parallel to the control curves in the presence of concentrations of DMI up to 3×10^{-6}M and that the effects of DMI were reversible suggested that the antagonism between DMI and each of the two agonists might be competitive. The nature of the antagonism was further tested by examining the relationship between log (x−1) and log B (where x is the mean value of the dose ratio obtained in the presence of a B molar concentration of DMI) using the data obtained with each agonist on both innervated and denervated arteries. Arunlakshana & Schild (1959) showed that for competitive antagonism the plot of log (x−1) against negative log B gives a linear relationship with a slope of −1. The line intercepts the abscissa at a point corresponding to the pA_2 for the antagonist (Schild, 1947). It follows from the equation of the line that when the slope is −1 the value of pA_2–pA_{10} is equal to 0·95.

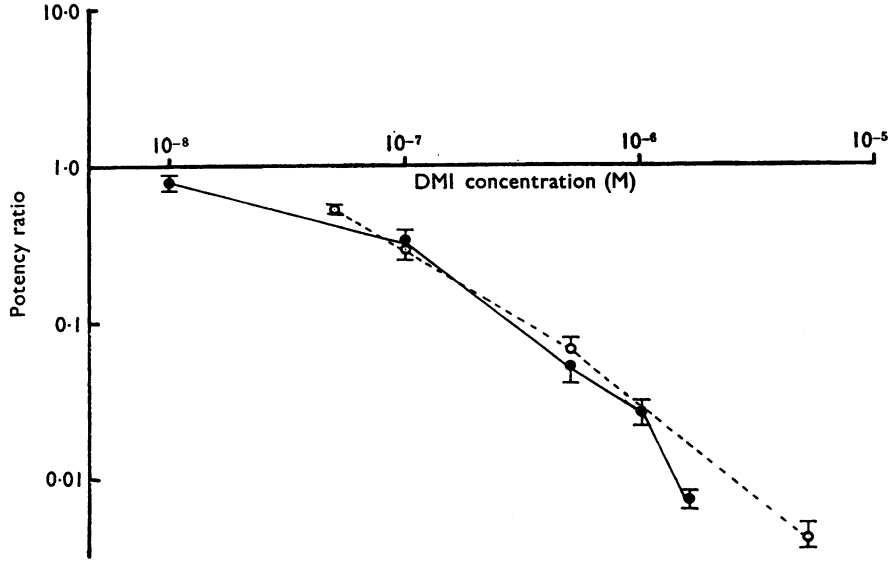

FIG 4. Effect of desipramine (DMI) on the responsiveness of innervated arteries (●) and sympathetically denervated arteries (○) to histamine. Potency ratios were calculated from the log concentration-response curves to histamine. The symbols represent the means and the vertical bars the standard errors of the means of data from 2 to 5 artery preparations for each concentration of DMI. Ordinates: potency ratio (logarithmic scale). Abscissae: molar concentration of DMI (logarithmic scale).

The slopes of the plots of log (x—1) against log B and the values of pA_2–pA_{10} for responses to NA and histamine in both innervated and denervated preparations are summarized in Table 1.

Noradrenaline

The plots obtained with the results from experiments in which noradrenaline was the agonist are shown in Figure 5. For both innervated and denervated arteries the relationship between log (x−1) and log B was linear ($P>0.05$). The slope of the line obtained with innervated arteries was 1·46 (95% confidence limits 1·002 to 1·91), and this value was significantly greater than 1·0 ($P<0.05$). The pA_2 value for the antagonism was 6·3. On the other hand, the slope of the line obtained

TABLE 1. *Analysis of the antagonism by DMI of the actions of noradrenaline and histamine using the method of Arunlakshana & Schild* (1959) *on rabbit ear arteries*

Agonist	Preparation	Slope*	pA_2–pA_{10}
Noradrenaline	Innervated	1·46 (1·002 to 1·91)	0·65 (0·5 to 0·948)
	Denervated	†1·02 (0·85 to 1·19)	0·93 (0·8 to 1·12)
Histamine	Innervated	1·34 (1·10 to 1·58)	0·71 (0·6 to 0·86)
	Denervated	1·19 (1·05 to 1·34)	0·80 (0·71 to 0·905)

* Slope of the plot of log (x–1) against log B; figures in parentheses are the 95% confidence limits.
† Not significantly different from 1·0 ($P>0.05$).

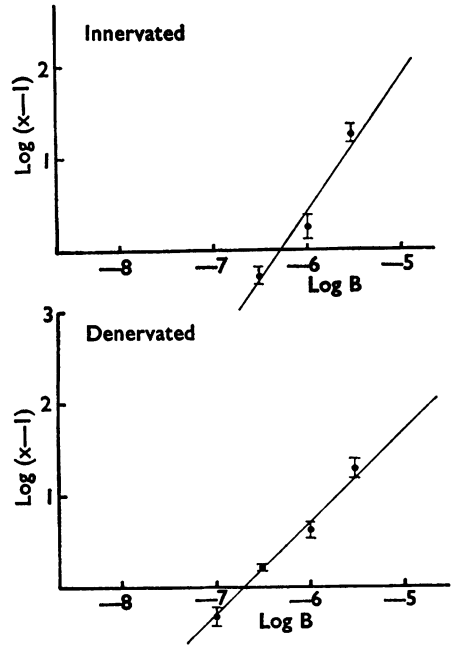

FIG. 5. Antagonism by desipramine (DMI) of responses to noradrenaline (NA) in innervated arteries (upper panel) and sympathetically denervated arteries (lower panel). Data from Fig. 1 have been plotted according to the method of Arunlakshana & Schild (1959). The ordinates are log (x—1), where x is the mean noradrenaline dose-ratio. The abscissae are log B, where B is the molar concentration of DMI. The lines are the calculated regression lines. For innervated arteries, the line intersects the abscissa at −6·3 (pA_2=6·3), the slope of the line is 1·46 (95% confidence limits: 1·002 to 1·91). For denervated arteries, the line intersects the abscissa at —6·7 (pA_2=6·7), and the slope of the line is 1·02 (0·85 to 1·19).

with the results from denervated arteries, 1·02 (0·85 to 1·19), was not significantly different from 1·0 ($P>0·05$). The pA_2 value for the antagonism by DMI of NA in denervated arteries was 6·7.

Histamine

A similar analysis of the results from experiments in which histamine was the agonist gave linear plots for both innervated and denervated preparations ($P>0·05$), as shown in Figure 6. In both cases the slopes of the lines differed significantly from the theoretical value of 1·0 for competitive antagonism ($P<0·05$). The pA_2 value for antagonism by DMI of histamine responses was 7·3 in both innervated and denervated preparations.

Discussion

A number of workers have demonstrated that DMI antagonizes the responses of certain isolated tissue preparations to exogenous NA and to sympathetic nerve stimulation (for references see **Introduction**). Such inhibitory effects of DMI have only been reported for tissues with α-adrenoceptors; however, it is not confined to responses produced by α-adrenoceptor agonists. Hrdina & Ling (1970) demonstrated that the action of $BaCl_2$ on the perfused renal artery of the rat was antagonized by DMI in a concentration-dependent manner, and in the present study the action of histamine on the perfused artery of the rabbit ear was antagonized by DMI.

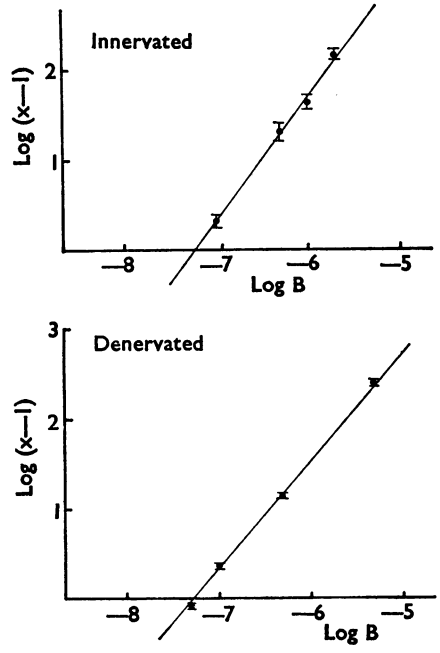

FIG. 6. Antagonism by desipramine (DMI) of the responses to histamine in innervated arteries (upper panel), and sympathetically denervated arteries (lower panel). Data from Fig. 4 have been plotted according to the method of Arunlakshana & Schild (1959). The axes are the same as in Figure 5. The lines are the calculated regression lines. For innervated arteries the line intersects the abscissa at $-7·3$ ($pA_2=7·3$) and the slope of the line is 1·34 (95% confidence limits 1·10 to 1·58). For denervated arteries the line intersects the abscissa at $-7·3$ ($pA_2=7·3$), and the slope of the line is 1·19 (1·05 to 1·34).

In innervated arteries, DMI in concentrations up to 1×10^{-7}M enhanced the responses to NA but with higher concentrations there was marked reduction of the responses. On the other hand, in sympathetically denervated arteries, DMI caused only antagonism of the vasoconstrictor responses to NA. Furthermore, with all but the highest concentration of DMI (3×10^{-6}M), the antagonism seen in the denervated preparations was significantly greater than that occurring in the innervated arteries. These findings are consistent with the generally accepted view that DMI enhances adrenergic responses by inhibition of the uptake of NA by sympathetic nerves (for references, see **Introduction**).

With all the concentrations studied and on both innervated and denervated arteries, DMI was considerably more potent in antagonizing the responses to histamine than the responses to NA. The magnitude of the antagonism of the vasoconstrictor action of histamine was essentially the same in both innervated and denervated arteries. It is unlikely therefore that histamine causes release of NA from sympathetic nerves such as occurs from the adrenal medulla (Feldberg & Lewis, 1964; Piper & Vane, 1967).

The inhibition by DMI of the responses to NA and histamine in both innervated and denervated arteries was associated with a concentration-dependent displacement to the right of the log concentration-response curves of the agonists. The log concentration-response curves remained parallel to the control curves even in the presence of concentrations of DMI which resulted in large displacements of the curves. Furthermore, the antagonism of both agonists by DMI was reversible. These findings suggested that the antagonism between DMI and NA and between DMI and histamine might be competitive.

Analysis of the data obtained in experiments in which NA was the agonist demonstrated that in denervated but not in innervated arteries the antagonism of responses to NA by DMI fulfilled the conditions for competitive antagonism as outlined by Arunlakshana & Schild (1959). The estimate of pA_2–pA_{10} for the antagonism of the action of NA by DMI in the denervated preparations, 0·93, was in close agreement with the theoretical value for competitive antagonism of 0·95. In innervated arteries, the corresponding value for pA_2–pA_{10} was 0·65, which is lower than the theoretical value for competitive antagonism. The apparent difference in the mechanism of the antagonism of NA by DMI in denervated and innervated preparations may be attributed to the counteracting potentiation of responses to NA by DMI due to inhibition of NA uptake in the innervated arteries. A similar suggestion was made by Arunlakshana & Schild (1959) to explain the low pA_2–pA_{10} value for the antagonism by atropine of the acetylcholine response of the guinea-pig ileum: it was attributed to a paradoxical potentiating effect of low concentrations of atropine. It is apparent from the present studies that, to obviate the complication of inhibition of neuronal uptake by DMI, quantitative studies of the receptor antagonism between DMI and NA must be carried out on sympathetically denervated tissues.

The depression of the maximal response to NA by DMI which occurred in both innervated and denervated arteries would not be consistent with the suggestion that DMI acted solely as a competitive antagonist. It is possible, however, that DMI antagonizes the action of NA in two ways: (i) by competitive antagonism of α-adrenoceptors; (ii) by a non-competitive but reversible inhibition of responses at a later stage in the excitation-contraction process. It would be necessary to postu-

late that the competitive component of the antagonism was the major factor in the horizontal displacement of the log concentration-response curves, whilst the non-competitive inhibition produced only slight shifts of the log concentration-response curves but was responsible for the depression in the maximal response to NA.

The antagonism of responses to histamine by DMI in both innervated and denervated arteries did not satisfy the theoretical requirements for competitive antagonism. The estimate of pA_2–pA_{10} for the innervated preparations was 0·71 and for the denervated preparations the value was 0·80, these figures being lower than the theoretical value for competitive antagonism. However, the pA_2 value for the antagonism between DMI and histamine was 7·3 in both innervated and denervated arteries. This value is high enough to suggest that the antagonism by DMI of the action of histamine is reasonably specific. If the depression of the maximum of the NA log concentration-response curve is due to a non-specific antagonism by DMI at a site beyond the α-receptor, then this same action of DMI would be expected also to operate against other agonists, including histamine. Thus it is possible that there are two components to the DMI antagonism of histamine: (i) reversible antagonism of histamine receptors, which would constitute a specific non-competitive antagonism and account for the major part of the displacement of the log concentration-response curves to histamine; (ii) reversible non-specific inhibition which would account for the depression of the maximal responses.

Hrdina & Ling (1970) suggested that the inhibition by DMI of contractile responses in the perfused rat renal artery to NA and $BaCl_2$ could be due to an action of DMI in decreasing the availability of Ca^{++} to intracellular sites associated with the contractile process. The results obtained in the present study would suggest that more than one site of action is involved in the antagonism by DMI of excitatory agents acting on the vascular smooth muscle of the rabbit ear artery. However, it is possible that the non-specific inhibitory action of DMI which has been put forward to explain the present findings might involve a mechanism such as that suggested by Hrdina & Ling.

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