The dopamine receptor antagonist domperidone is also a competitive antagonist at α_1-adrenoceptors

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It has previously been reported that domperidone selectively antagonized the relaxation produced by dopamine on the guinea-pig isolated gastroesophageal junction, (Ennis et al 1978). The dopamine receptor antagonists spiroperidol and haloperidol, but not pimozide and metoclopramide, also showed some selectivity in inhibiting only the response to dopamine and not the response to noradrenaline, which produced a relaxation followed by a contraction on this preparation. However the response to dopamine on the guinea-pig isolated gastroesophageal junction could also be antagonized by the α_1-adrenoceptor antagonist prazosin (Cox & Ennis 1980). A possible explanation for this apparent selective antagonism by domperidone therefore was that in addition to its known ability to block dopamine receptors in vitro (Van Nueten & Janssen 1978) it may also have the ability to block α_1-adrenoceptors since both spiroperidol and haloperidol are claimed to possess some α_1-adrenolytic activity.

This study was designed therefore to compare the potency of domperidone as an antagonist at α_1-adrenoceptors with a series of α_1-adrenoceptor and dopaminoceptor antagonists. The guinea-pig aortic strip preparation was used in these experiments to maintain continuity of species, since guinea-pig gastrointestinal tissue had been used for all previous experiments with domperidone.

Guinea-pigs of either sex, 300–500 g, were killed by a blow to the head. The thoracic aorta was removed, cut into spiral strips 3 cm in length and set up for isometric recording of tension changes in Krebs-Henseleit solution maintained at 37 °C and aerated with 5% carbon dioxide in oxygen. Cumulative concentration-effect curves were constructed to phenylephrine. Antagonists were added to the bathing fluid during the washing period after a control concentration-effect curve had been established. Subsequent concentration-effect curves were performed in the presence of the antagonist with a minimum equilibration period of 30 min. Arunlakshana-Schild plots were made to allow the calculation of pA_2 values.

The drugs used were: domperidone, haloperidol (Haldol), pimozide, spiroperidol (spiperone) (Janssen Pharmaceutica); metoclopramide, (Beecham Pharmaceuticals); phentolamine mesylate, (BDH); phenylephrine hydrochloride, (Sigma) and prazosin hydrochloride, (Pfizer).

Phenylephrine, an α_1-adrenoceptor agonist, produced a concentration-related increase in tension of the aortic strip over the concentration range 2×10^{-7} to 2×10^{-4} M with an ED50 of 10^{-6} M. Over 6 h this concentration-effect curve was shown to be reproducible, subsequent curves being superimposable (Fig. 1). At these concentrations the β-adrenoceptor activity of the drug was negligible.

In the presence of increasing concentrations of the α-adrenoceptor antagonists phentolamine and prazosin, parallel rightward shifts of the concentration-effect curve to phenylephrine were obtained. Domperidone (Fig. 1) and the butyrophenone neuroleptics haloperidol and spiroperidol also produced parallel rightward shifts in the concentration-effect curve to phenylephrine. However, pimozide had no effect in concentrations up to 10^{-6} M, at which concentration it has been shown to produce non-specific antagonism of acetylcholine (Ennis et al 1979). Metoclopramide in doses up to 5×10^{-5} M also had no effect on the response of the aorta to phenylephrine.

When the pA_2 values were calculated (Table 1) it was found that prazosin was the most potent antagonist tested, having a pA_2 value of 9·0. Phentolamine, had a pA_2 value of 7·8 which was significantly less than the

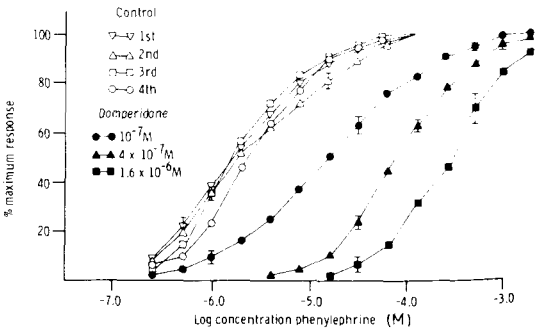

FIG. 1. Effect of domperidone on the cumulative dose-response curve to phenylephrine on the guinea-pig aortic strip preparation.

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Table 1. pA_2 values of a series of compounds as antagonists of the contractions produced by phenylephrine on the guinea-pig aorta (n = 5)

Compound	pA_2 value ± s.e.m.*
Prazosin	9·0 ± 0·1
Phentolamine	7·8 ± 0·2
Domperidone	7·4 ± 0·1
Spiroperidol	8·8 ± 0·1
Haloperidol	6·6 ± 0·1
Pimozide	No effect
Metoclopramide	No effect

* For significance of differences see text

pA_2 value of prazosin ($P < 0·01$, Mann-Whitney U test, 2 tailed). Domperidone had a pA_2 value of 7·4 which was not significantly different from that for phentolamine. Spiroperidol was also a potent antagonist having a pA_2 value of 8·8 which was not significantly different from the results for prazosin. The pA_2 value for haloperidol was significantly less than that for domperidone, being 6·6. Thus the relative order of potency for the antagonists tested was: prazosin > spiroperidol > phentolamine > domperidone > haloperidol, with pimozide and metoclopramide being ineffective as antagonists of phenylephrine.

The aorta is known to contain α_1-adrenoceptors which are poorly innervated. This fact, together with the use of phenylephrine as an agonist, provided the optimum conditions for the investigation of α_1-adrenoceptor antagonism as there would be no uptake of agonist into the tissue which could represent a source of loss of the agonist during the experiment which may cause an error in the calculation of antagonist potency, (Furchgott 1972). The guinea-pig aorta proved to be an ideal tissue for this investigation because repeated concentration-effect curves to phenylephrine were superimposable.

Since the antagonists which were effective produced parallel rightward shifts with no inhibition of the maximum response to phenlephrine, the application of Arunlakshana-Schild plots to obtain a relative order of antagonist potency was valid.

Prazosin was the most potent antagonist tested. It has been reported to be a specific and potent α_1-adrenoceptor antagonist (Cambridge et al 1977). Phentolamine which is less specific for α_1-adrenoceptors than prazosin had a much lower pA_2 value. Some of the dopamine antagonists had pA_2 values of the order of prazosin and phentolamine. The relative order of potency of these dopamine antagonists as antagonists at α_1-adrenoceptors was: spiroperidol > domperidone > haloperidol. This is similar to their order of potency as inhibitors of tritiated haloperidol binding and thus as antagonists at dopamine receptors. However the two exceptions from the correlation were pimozide and metoclopramide, both of which were effective dopamine antagonists as measured by inhibition of tritiated haloperidol binding (Leysen et al 1978) but which did not antagonize the response to either phenylephrine on the guinea-pig aorta or dopamine on the guinea-pig gastroesophageal junction.

The fact that domperidone was as effective as phentolamine as an antagonist of phenylephrine on the aorta demonstrates that it possesses α_1-adrenoceptor blocking properties in addition to its reported dopamine receptor blocking activity. This α_1-adrenolytic activity may be the reason for the block of dopamine on the gastroesophageal junction since only those dopamine antagonists which blocked the response to phenylephrine on the aorta also antagonized the response to dopamine on the gastro-oesophageal junction. Thus, if domperidone is to be used as a tool to investigate dopamine receptor mechanisms, care should be taken to avoid the possibility that α_1-adrenoceptors are not also involved.

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