prostatic but not in the epididymal portion this inhibition was antagonised by sotalol. At least part of this β-effect was post-junctional since phenylephrine-induced contractions were inhibited. Isoprenaline also produced an α_1-mediated excitation in the epididymal portion.

Other agonists: ATP and (D-Ala^2, D-Leu^5)-enkephalin, produced pre-junctional inhibition in each portion which was independent of adrenoceptors. The effect of ATP was greater on the prostatic portion while that of (D-Ala^2, Leu^5)-enkephalin was similar in each portion and could be reversed by naloxone.

With each of these examples the precision of the observations was increased by analysing separately the responses of the different portions. Furthermore the adrenergic and 'non-adrenergic' components need no longer be inextricably confused. These results may, therefore, justify the introduction of limited, double-blind classroom trials with a view to rehabilitation of the preparation.

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Mechanism of action of dopamine on the guinea-pig isolated gastroesophageal junction

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Domperidone has been shown to block central dopamine receptors but after peripheral administration it does not readily cross the blood brain barrier (Costall, Fortune & Naylor, 1979). This has led to the suggestion that its gastrointestinal effects are due to an interaction with a peripheral dopaminergic system (Van Nueten & Janssen, 1978). A selective effect of domperidone on dopamine-induced relaxations of the isolated longitudinal muscle strip of the guinea-pig gastroesophageal junction has been reported (Ennis, Schnieden & Cox, 1978). We have examined the ability of a series of dopamine antagonists to inhibit the response to dopamine on the gastroesophageal junction and phenylephrine on the isolated aortic strip using the pA_2 method of Arunlakshana & Schild (1959). These compounds had no effect on the relaxations of the gatroesophageal junction induced by either isoprenaline or noradrenaline. Whilst the relative order of potency for spiroperidol, domperidone and haloperidol on the gastroesophageal junction was that which would be predicted for an interaction with dopamine receptors (Table 1), pimozide and metoclopramide were ineffective. These results do not support the suggestion of a peripheral dopamine system in the gastrointestinal tract.

There appeared to be a close correlation between the ability to block the α_1 adrenoceptor of the aorta

Table 1 Comparison of pA_2 values for a series of dopamine receptor blocking drugs as antagonists of dopamine on the gastroesophageal junction and phenylephrine on the spiral aortic strip of the guinea-pig

	pA_2 value	
Antagonist	*Gastroesophageal Junction*	*Aortic Strip*
Spiroperidol	8.6 ± 0.3	8.8 ± 0.1
Domperidone	6.6 ± 0.1	7.4 ± 0.1
Haloperidol	6.1 ± 0.1	6.6 ± 0.1
Pimozide	No antagonism	No antagonism
Metoclopramide	No antagonism	No antagonism

and the ability to inhibit dopamine-induced relaxations of the gastroesophageal junction. Similarly the selective α_1 adrenoceptor antagonist prazosin (Cambridge, Davey & Massingham, 1977), gave pA_2 values of 8.6 ± 0.2 and 9.0 ± 0.1 on the gastroesophageal junction and aorta respectively, indicating that the gastrointestinal effects of domperidone are more likely to be mediated by an interaction with α-adrenoceptors. The dopamine antagonists did not inhibit noradrenaline-induced relaxations of the gastroesophageal junction pointing to a difference in the mode of action of noradrenaline and dopamine on this tissue. This is an aspect of the study requiring further investigation.

C.E. is an SRC CASE award student.

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The effects of Cd^{2+} on the myogenic activity and the responsiveness of the rat portal vein to perimural stimulation, noradrenaline and potassium ions

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Cd^{2+} have been shown to inhibit the responses of rat vas deferens and anococcygeus muscles preparations to noradrenaline (NA), tyramine, K^+ and perimural stimulation, NA being the least effected (Fadloun & Leach, 1979). In the present study the responses of the rat portal vein have been studied, since it possesses myogenic activity which is independent of its sympathetic innervation.

Rat portal veins were prepared using the method described by Johansson & Ljung (1967). Special tissue holders were used to allow adequate superfusion and perimural stimulation (Fadloun & Leach, 1978). The superfusion rate was 3 ml/min using Krebs solution at 37°C aerated with 95% O_2/5% CO_2. The stimulation parameters used were: 20 V, pulse width 0.1 ms, 1–25 Hz with a stimulation period of 1 minute. The effects of NA (10–160 ng) and K^+ (5–40 μM) were also tested.

The tissue responses to perimural stimulation were found to be biphasic. Cd^{2+} (0.5–2 μM) were shown to reduce the amplitude of the spontaneous phasic contractions Cd^{2+} (0.5 μM) increased the frequency of the phasic contractions by approximately 25%, whilst Cd^{2+} (2 μM) failed to change the frequency, but reduced the amplitude to approximately 50% of the control.

Cd^{2+} (0.5–2 μM) were also found to inhibit the responses to perimural stimulation, the first phase being more effected. Low frequencies (1–12 Hz) were more effected than the higher frequency (25 Hz). In addition, Cd^{2+} were also shown to inhibit the contractions caused by small doses of K^+ (5–20 μM). However, Cd^{2+} (0.5 μM) did not affect NA responses, but at 2 μM the inhibition ranged between 40% and 10% according to the dose tested (10 ng and 160 ng respectively).

Responses to perimural stimulation, K^+ and NA were reduced when the Ca^{2+} concentration of the Krebs solution was reduced (1.27 mM) and 0.635 mM). The responses to perimural stimulation and smallest doses of K^+ were most effected. No myogenic activity was seen at Ca^{2+} (0.635 mM).

The inhibitory effects of Ca^{2+} (1.27 mM) and Cd^{2+} (0.5 μM) were found to be synergistic to all three tests.

Cysteine (0.5 mM), administered when the effect of Cd^{2+} (2 μM) had been established, partially restored the responses inhibited by Cd^{2+}. Cysteine significantly increased the frequency of the phasic contractions but did not affect the amplitude; this was found to be similar to the effect of restoration to normal Krebs after using Ca^{2+} (0.635 mM). Yohimbine (10 ng/ml) potentiated the responses to perimural stimulation at all frequencies (1–25 Hz), but did not affect NA (10 ng–160 ng) responses at the same concentration.

The results obtained in the sympathetically innervated vascular muscle preparation are in close agreement with previous studies using non-vascular preparations (Fadloun & Leach, 1979), suggesting that Cd^{2+} possess a higher affinity towards presynaptic sites, possibly by interference with the intracellular Ca^{2+} mobilisation.