the sympathetic responses. In contrast the pressor response reached its peak within 0.5 min but had disappeared by 8 min although the plasma levels of clonidine were virtually unchanged over this period and the response to a subsequent injection of clonidine or noradrenaline was unaffected. Similarly in the anococcygeus the contraction by clonidine was shorter-lived than the presynaptic inhibitory effect.

In conclusion, (i) all monitored effects of clonidine had an equally rapid onset, (ii) the duration of prejunctional inhibition was related to plasma clonidine levels, (iii) the short-lived post-junctional effects were related to the initial high concentration due to the injection of a bolus.

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Estimation of dissociation constants and relative efficacies of isoprenaline, orciprenaline and terbutaline in guinea-pig isolated atria by use of functional antagonism

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Affinity values for antagonists indicate that the β-adrenoceptors mediating positive inotropic and chronotropic responses of isolated atria are identical (Blinks, 1967; Lumley & Broadley, 1975). However, agonists exhibit selective chronotropic activity and partial agonists have lower maxima for the tension response (Lumley & Broadley, 1977). To determine the possible source of these differences, both dissociation constants and relative efficacies must be determined (Jenkinson, 1973). We have used functional antagonism (Van den Brink, 1973; Buckner, Torphy & Costa, 1978) in isolated guinea-pig atria to calculate these parameters for isoprenaline, orciprenaline and terbutaline.

Rate responses were obtained from isolated right atria and tension responses from paced left atria (2 Hz), set up at 38°C in Krebs-bicarbonate solution gassed with 5% CO_2 in O_2. Cumulative dose-response curves to isoprenaline were followed by orciprenaline or terbutaline curves. The mean (n = 4) orciprenaline (100.5 ± 3.99%) and isoprenaline rate maxima did not differ significantly, but the orciprenaline tension (92.3 ± 0.35%) and terbutaline rate (84.4 ± 4.8%) and tension (58.2 ± 2.62%) maxima were significantly less ($P < 0.05$). These terbutaline maxima differed significantly ($P < 0.01$).

To determine the dissociation constants of these agonists, cumulative dose-response curves to isoprenaline and either orciprenaline or terbutaline were constructed before and in the presence of carbachol (200 nM) as the functional antagonist. Responses were measured as increase above their own resting levels and plotted as a percentage of the pre-carbachol isoprenaline maximum against log molar concentration. All experiments were corrected for sensitivity changes from control experiments (n = 4). The affinities were obtained from double reciprocal plots of equiactive molar concentrations before and after carbachol. These yielded the dissociation constant K_a as slope –

1/intercept (Furchgott, 1966). The K_a values for isoprenaline (n = 8), orciprenaline (n = 4) and terbutaline (n = 4) were 6.25×10^{-8}, 7.57×10^{-6} and 11.31×10^{-4} M on rate and 8.96×10^{-8}, 5.48×10^{-6} and 7.67×10^{-4} M respectively on tension. There was therefore no difference in affinity of these agonists for the β-adrenoceptors mediating rate and tension responses.

The efficacy of orciprenaline and terbutaline relative to isoprenaline were determined by replotting the initial dose-response curves for the agonist compared with isoprenaline. The response to each concentration of agonist was plotted against the negative logarithm of the fraction of active receptors (RA/Rt) occupied by the agonist ($RA/Rt = A/K_a + A$). The relative efficacy was the antilogarithm of the distance between the agonist curve and corresponding isoprenaline curve along the RA/Rt axis. Terbutaline (1.33) and orciprenaline (1.78) had greater relative efficacy values than isoprenaline on rate, in spite of their lower affinities. Indeed, in the presence of carbachol, orciprenaline produced a greater maximum response than isoprenaline. This confirms the suggestion of O'Donnell & Wanstall (1977). On tension, their relative efficacies were lower than isoprenaline (orciprenaline 0.56; terbutaline 0.21) and this may explain their lower maxima on tension than on rate. The replotted rate curves for all agonists were to the left of those for tension which may indicate that their rate selectivity is due to a greater efficacy.

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A study on potassium-depolarized trachael chain preparations from guinea-pigs

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The extraneuronal uptake (ENU) inhibitor drugs phenoxybenzamine (PHB) and metanephrine (MN) potentiated responses to isoprenaline on guinea-pig tracheal chain preparations (O'Donnell & Wanstall, 1976) but not on guinea-pig uterine preparations (Anning, O'Donnell & Wanstall, 1978). The uterine preparations, unlike the tracheal preparations, were depolarized by immersion in K^+-Krebs solution (Krebs solution in which all the sodium was replaced by the equivalent amount of potassium) in order to induce tone. Fluorescence histochemical experiments indicated that the smooth muscle of both trachea and uterus could accumulate isoprenaline extraneuronally, but in both tissues the accumulation was markedly reduced if K^+-Krebs solution was used instead of normal Krebs solution (Anning *et al.*, 1978). Thus it was postulated that the failure of ENU inhibitor drugs to potentiate isoprenaline responses on K^+-depolarized uterine preparations was due to the use of the K^+-Krebs solution. The present study was carried out to see if data to substantiate this hypothesis could be obtained on trachea. Therefore pharmacological experiments have been carried out using K^+-depolarized tracheal chain preparations from guinea-pigs. In particular the effects of PHB or MN on responses to isoprenaline on K^+-depolarized tracheal