Thus when θ is 90°, the velocity is zero, whilst maximum velocity (ωr) is achieved when θ is 0°.

From a knowledge of the speed of rotation of the shaft, and the time interval represented by each line on the computer printout, the angular displacement θ and hence the punch velocity can be calculated for any point in time represented by a given line on the computer printout.

Hence the overall power expended can be calculated by summation of the products of the force and the corresponding velocity.

The use of power, involving as it does the speed of application of the force, also satisfies the requirement that in the case of substances which consolidate by fragmentation, the kinetic energy of the moving punch will obviously influence the degree of particle fracture.

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α_2-Adrenoceptors and the delay of castor oil-induced diarrhoea by clonidine in rats

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Although clonidine has been reported to inhibit castor oil-induced diarrhoea in rats (Lal et al 1981; Lal & Shearman 1981), the receptor type involved in this action of clonidine has not been characterized. Clonidine has been shown to be an α-adrenoceptor agonist, acting predominantly at α_2-receptors, but also having some α_1-agonist activity (Drew 1981; Doxey et al 1981). We have investigated the α-adrenoceptor subtype involved in the antidiarrhoeal action of clonidine using phenylephrine, an agonist acting at α_1-adrenoceptors (Drew 1981), prazosin, a potent α_1-adrenoceptor antagonist and yohimbine, an α_2-adrenoceptor antagonist (Drew 1981; van Meel et al 1981).

Method

Male wistar rats (approximately 200 g) were starved overnight, but allowed free access to water. The rats were injected intraperitoneally (i.p.) with 0·9% NaCl (saline) (1 ml kg^{-1}; control) or with the appropriate test drug(s). Thirty min later, each rat was dosed orally with 2 ml of castor oil and was then observed at 30 min intervals for up to 6 h for the onset of diarrhoea. This was defined as the appearance of unformed faeces and perianal staining of the fur. The data have been expressed as time to onset of diarrhoea for individual rats, with the median for each group. Statistical analysis was made using the Mann-Whitney U-test for unpaired data, as described by Siegel (1956). Two-tailed tests were used and a P value of less than 0·05 was considered to be significant. The drugs used were: clonidine (Boehringer Ingelheim Ltd.), phenylephrine (Koch-Light Laboratories Ltd), yohimbine (Sigma Chemical Co. Ltd), prazosin (Pfizer Ltd) and castor oil (BDH Chemicals Ltd).

Results

All control rats developed diarrhoea within 2 h of castor oil treatment (Fig. 1). Clonidine from 0·1 to 1·0 μmol kg^{-1} i.p. caused a dose-related delay of the onset of diarrhoea, with the highest dose preventing diarrhoea for greater than 6 h (Fig. 1). In contrast, high doses of phenylephrine (1 to 100 μmol kg^{-1} i.p.) failed to delay the onset of castor oil-induced diarrhoea (Fig. 1).

A dose of clonidine of 0·3 μmol kg^{-1} i.p., which produced a statistically significant, but submaximal delay of diarrhoea was used to investigate the effects of α-adrenoceptor antagonists. The results of these experiments are shown in Fig. 2. Yohimbine (1 to 10 μmol kg^{-1} i.p.) produced a dose-related reversal of the clonidine-induced delay of diarrhoea, the highest dose of yohimbine completely prevented clonidine's effects. In contrast, prazosin (3 to 30 μmol kg^{-1} i.p.) caused no significant reversal of clonidine's antidiarrhoeal effect. Yohimbine (10 μmol kg^{-1} i.p.) and prazosin (30 μmol kg^{-1} i.p.) alone (in the absence of

* Correspondence.

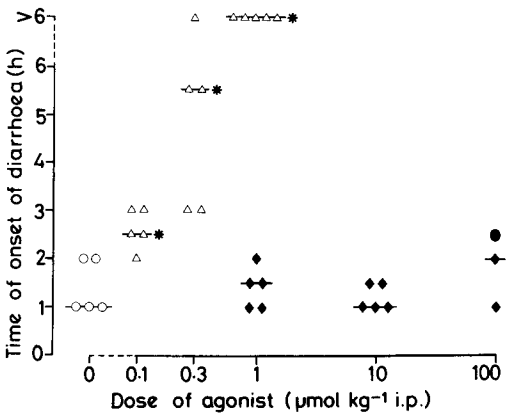

FIG. 1. The effects of clonidine and phenylephrine on the onset of castor oil-induced diarrhoea. Individual results are shown, with horizontal lines denoting the medians of groups. ○: Saline pretreated rats (control). △: Clonidine pretreated rats. ◆: Phenylephrine pretreated rats. * : P <0·05, compared with control group.

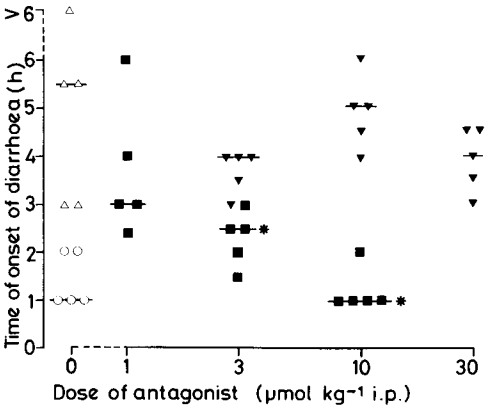

FIG. 2. The effects of yohimbine and prazosin on the delay of castor oil-induced diarrhoea caused by clonidine (0·3 μmol kg⁻¹ i.p.). Individual results are shown with horizontal lines denoting the medians of groups. ○: Saline pretreated rats (control)†. △: Clonidine pretreated rats†. ■: Yohimbine + clonidine pretreated rats. ▼: Prazosin + clonidine pretreated rats. * : P <0·05, compared with clonidine group. †: These data are also presented in Fig. 1.

clonidine) had no significant effect on the time of onset of castor oil-induced diarrhoea, with all rats developing diarrhoea between 1 and 2.5 h.

Discussion

We have shown that clonidine produced a dose-related inhibition of castor oil-induced diarrhoea in the conscious rat in a range of 0·1 to 1·0 μmol kg^{-1} i.p. Similar doses of clonidine were reported by Lal et al (1981) to inhibit diarrhoea in the same animal model and by Nakaki et al (1982a, 1982b) to inhibit intestinal secretion induced by cholera toxin and prostaglandin E_1 in anaesthetized rats.

Comparison of these antidiarrhoeal doses of clonidine and those reported to exert cardiovascular effects in the rat is complicated by the different routes of administration used. However, it seems that much larger doses of clonidine are required for antidiarrhoeal activity, since a dose of only 6 nmol kg^{-1} i.v. caused a 50% inhibition (by an interaction with α_2-adrenoceptors) of the tachycardia induced by sympathetic nerve stimulation (van Meel et al 1981). Despite the relatively large doses of clonidine required for its antidiarrhoeal activity, such effects do not appear to be mediated by α_1-adrenoceptors, since large doses of the α_1-agonist phenylephrine did not significantly delay the onset of castor oil-induced diarrhoea. For comparison, phenylephrine increases diastolic blood pressure (by an interaction with α_1-adrenoceptors), with an ED50 of 26 nmol kg^{-1} i.v. (van Meel et al 1981). Furthermore, the antidiarrhoeal effects of clonidine were not reversed by large doses (approximately 10 to 30 times those used in cardiovascular studies) of the α_1-adrenoceptor antagonist prazosin (Drew 1981; van Meel et al 1981), but were reversed by the α_2-adrenoceptor antagonist yohimbine, in doses similar to those exhibiting α_2 blocking activity in the cardiovascular system (van Meel et al 1981).

This latter result, taken with the lack of effect of high doses of phenylephrine and prazosin, is consistent with the view that clonidine's antidiarrhoeal activity in castor oil-treated rats is mediated by α_2-adrenoceptors, and further evidence in support of this hypothesis might be obtained using more selective α_2-adrenoceptor agonists and antagonists.

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