depend on the proximity of the pump to the patient's body, and the effect of bedclothes and other coverings. It is possible that precipitation may occur in the syringe driver or the infusion pump. This could result in loss of pain control because of inadequate delivery of diamorphine. Clinical experience with *long-term* infusion of diamorphine is limited but we have experienced no problems with infusions maintained for up to two weeks (Jones & Hanks 1986).

The observed changes in pH and liberation of acetic acid may also have clinical implications. Local irritation at the site of infusion is well recognized and may be more common when high doses of diamorphine are used (Regnard & Newbury 1983).

In general, diamorphine solutions for infusion are freshly made up and used within 24 h. There is increasing interest in the use of longer-term infusions both by the subcutaneous route and by the spinal route, where the implications of precipitation and local irritation are potentially more serious. The results of the present work demonstrate the need for caution in using high concentrations of diamorphine in this way. Careful regular examination of the syringe for signs of precipitation is recommended.

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Evidence for α_1-adrenoceptor subtype predominance in the rat seminal vesicle

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Abstract—Noradrenaline (0·6–19 μM) and phenylephrine (2–130 μM) induced contractions in the rat seminal vesicle that were competitively antagonized by the α_1-adrenoceptor-selective antagonist corynanthine (120–920 nM). Yohimbine (60–450 nM), an α_2-adrenoceptor-selective antagonist, produced a non-competitive antagonism of noradrenaline responses, suggesting that the responses were not α_2-adrenoceptor mediated. It is concluded that the rat seminal vesicle has a predominance of α_1-adrenoceptors.

The presence in the rat seminal vesicle of post junctional α-adrenoceptors has been well demonstrted (Saxena 1970; Castelli & Genedani 1982; Hib et al 1984). It is widely believed that post-junctional α-adrenoceptors exist as two subtypes, namely the α_1- and α_2-adrenoceptors (Moulds & Jauernig 1977; Drew & Whiting 1979; Docherty & McGrath 1980; Adenekan & Tayo 1982, 1985). The studies on the rat seminal vesicle have provided little or no information about the subtype(s) of post-junctional α-adrenoceptors present in the preparation. I have examined the interactions of noradrenaline and phenylephrine with antagonists in the rat seminal vesicle in an attempt to characterize the α-adrenoceptor subtypes.

Methods

Male albino rats, 200–250 g were stunned and exsanguinated. Both seminal vesicles were isolated, desheathed and the lumen well flushed out with Tyrode solution. Each seminal vesicle was mounted under a resting tension of 1·0 g in a 15 mL organ bath containing Tyrode solution of the following composition (mmol L^{-1}): NaCl 136·9, KCl 2·7, $CaCl_2$ 1·8, $MgCl_2$ 0·9, NaH_2PO_4 0·3, $NaHCO_3$ 11·9 and glucose 5·6. The Tyrode solution was maintained at 36°C and gassed with air while the tissue was connected through an Ugo Basile DY2 force-displacement transducer to a 'Gemini' recorder. After 60 min equilibration, during which the Tyrode solution was replaced at 15 min intervals, non-cumulative concentration-response curves were constructed repeatedly in the absence (control) or presence of three increasing antagonist concentrations. A tissue-drug contact time of 30 s was allowed and the tissue rested for 4 min between contractions. Each antagonist concentration was allowed 25 min equilibration time with the tissue before the agonist was added. Control tissues showed no significant changes in the concentration-response curves over the period of experiment. All experiments were carried out in the presence of cocaine (1·3 μM) to block neuronal uptake. The pA_2 values of the antagonists were estimated by Schild regression plots and antagonism was regarded as competitive when the slope of the Schild regression line was not significantly different from unity (Arunlakshana & Schild 1959). The significance of the differences was analysed with Student's *t*-test and the accepted level of significance was $P < 0.05$.

Drugs used were: Noradrenaline hydrochloride, phenylephrine hyrochloride, yohimbine hydrochloride, corynanthine hydrochloride (Sigma) and cocaine hydrochloride (Krakowski Zargad, Poland). Concentrations refer to base.

Results

Noradrenaline (NA) (0·6–19 μM) and phenylephrine (PE) (2–130 μM) produced concentration related contractions of the rat seminal vesicle unlike UK-14, 304–18 (0·3–76 μM), B-HT 920 (2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*d*]azepine dihydrochloride) and B-HT 933 (2-amino-6-ethyl-4,5,7,8-tetrahydro-6*H*-oxazolo-[5,4-*d*] azepine dihydrochloride) (3·6–920 μM) which did not evoke any contractions. Corynanthine (120–920 nM) produced competitive antagonism of NA and PE as revealed by the Arunlakshana and Schild (A–S) plots. It had pA_2 values of

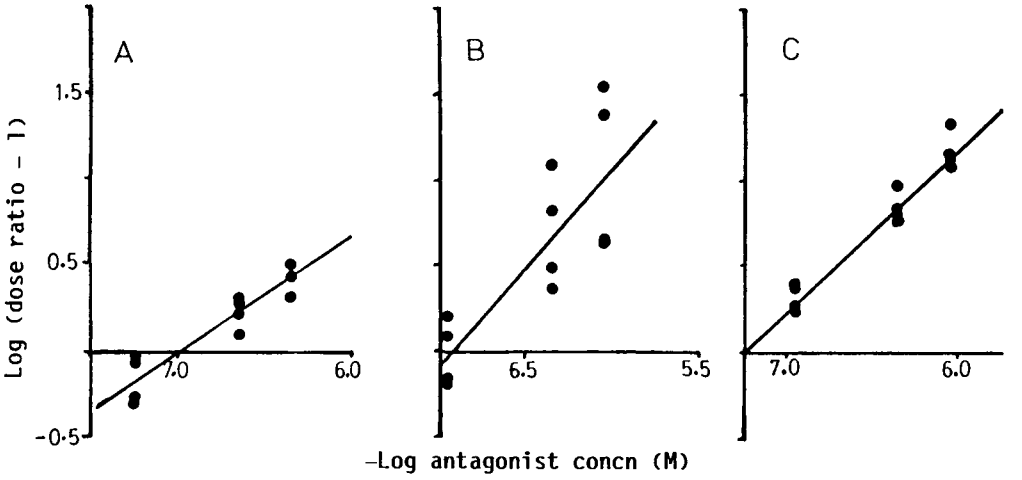

FIG. 1. Schild regression lines for (A) yohimbine antagonism of noradrenaline (slope = 0·67 ± 0·09), (B) corynanthine antagonism of noradrenaline (slope = 1·17 ± 0·27 and pA_2 6·92 ± 0·09) and (C) corynanthine antagonism of phenylephrine (slope = 0·96 ± 0·06 and pA_2 = 7·25 ± 0·02). Values were obtained by regression analysis of 12 data pairs (see Tallarida et al 1979).

6·92 ± 0·09 (Slope = 1·17 ± 0·27) and 7·25 ± 0·02 (Slope = 0·96 + 0·06) against NA and PE, respectively (Fig. 1). Yohimbine (60–450 nM) produced a non-competitive antagonism of NA contractions, the slope of the A–S plot (0·67 ± 0·09) being significantly different from unity ($P < 0·05$, n = 12). Prazosin (1 nM–0·1 μM) produced rightward but non-parallel shifts of NA and PE concentration-response curves; the maximal response decreasing with increasing prazosin concentration.

Discussion

Yohimbine, a selective α_2-adrenoceptor antagonist was matched against NA, a non-selective α_2-adrenoceptor agonist, to investigate α_2-adrenoceptor involvements since the available α_2-selective agonists (UK–14, 304–18, B-HT 920 & 933) had no visible effects on the seminal vesicle. PE and corynanthine, α_1-adrenoceptor selective agonist and antagonist, respectively, were used for α_1-adrenoceptor studies. Prazosin, the preferred α_1-antagonist was not useful because of its non-parallel shifts of the agonist concentration-response curves. The competitive nature of corynanthine's antagonism of PE contractions suggested α_1-adrenoceptor mediation of the response. The failure of yohimbine to competitively antagonize competition (A–S slope 1) responses to NA indicates that NA is not acting through α_2-adrenoceptors (see Kenakin 1985). Corynanthine produced a competitive antagonism of NA contractions, indicating α_1-adrenoceptor mediation. Thus, it would be expected that corynanthine should produce similar pA_2 values against the full agonists NA and PE, if indeed all three drugs were acting on the same receptor type (Schild 1947). However, the pA_2 values (7·25 ± 0·02 and 6·92 ± 0·09) produced by corynanthine against PE and NA, respectively, were significantly different ($P < 0·05$, n = 12). This may suggest that the receptor population is not homogenous but that there is a small corynanthine-resistant population participating in the mediation of NA induced contractions which renders corynanthine 'less potent' (lower pA_2) against NA.

In conclusion, it seems the α-adrenoceptor population in the rat seminal vesicle is predominantly of the α_1-subtype.

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