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Ketamine-inhibition of calcium-induced contractions in depolarized rat uterus: a comparison with other calcium antagonists

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1 The inhibitory effect of the intravenous anaesthetic ketamine on $CaCl_2$-induced contractions in the isolated K^+-depolarized uterus of the rat in Ca^{2+}-free medium was compared with that produced by papaverine, theophylline and the calcium entry blocker verapamil.

2 Pre-incubation for 20 min with either ketamine (0.3 to 3 mM), papaverine (3 to 30 μM), theophylline (0.1 to 1 mM) or verapamil (3 to 30 nM) induced parallel, concentration-dependent rightward displacements of the dose-response curves to Ca^{2+} (0.04 to 22 mM). The antagonism was competitive, except that due to verapamil, the Schild plot for which yielded a slope which differed significantly from unity. The calculated pA_2 values (± s.e.mean) were: ketamine 3.90 ± 0.07; papaverine 5.55 ± 0.05; theophylline 3.99 ± 0.1 and verapamil 9.54 ± 0.24

3 These drugs differed in their ability to relax the sustained contraction induced by Ca^{2+} (1 mM) in K^+-depolarizing solution. Ketamine and verapamil relaxed the preparation in a concentration-dependent manner whereas theophylline and especially papaverine were less potent and induced only partial maximal relaxation. The $t_{\frac{1}{2}}$ of the relaxant effect was significantly less for ketamine than for verapamil (5 and 22 min, respectively). Only ketamine produced a relaxation comparable to that obtained by washing the preparation with Ca^{2+}-free solution ($t_{\frac{1}{2}}$ = approx. 5 min).

4 Prior exposure of the depolarized uterine strip to a low concentration of Ca^{2+} (0.22 mM) increased the potency of ketamine, but decreased that of papaverine and theophylline, in antagonizing Ca^{2+}-induced contractions. In contrast, this procedure did not affect the potency of verapamil.

5 The inhibitory effects of these drugs, excluding those of verapamil, were completely reversed after washing the preparations with a high-potassium Ca^{2+}-free solution, 3–5 times for about 30–60 min.

6 These experiments provide further evidence that the relaxant effect produced by ketamine on the rat isolated uterus is due to its ability to antagonize Ca^{2+} movements competitively and also show that there are marked differences between the nature of the relaxant effects of ketamine and those of papaverine, theophylline and verapamil.

Introduction

Ketamine, an intravenous anaesthetic, relaxes drug-induced contractions in both vascular and non-vascular smooth muscle in concentrations comparable to those achieved in plasma during anaesthesia (Lundy *et al.*, 1974; 1975; Clanachan & McGrath, 1976; Altura *et al.*, 1980; Little *et al.*, 1983; Fukuda *et al.*, 1983).

Ketamine also inhibits agonist-induced contractions in the isolated, pregnant myometrium of several animal species, including man (Duarte *et al.*, 1979). Theophylline, but not lidocaine, enhances the inhibitory effect of ketamine. The relaxant effect of ketamine, papaverine and the calcium entry blocker verapamil, have been shown to be reversed by increasing the $[Ca^{2+}]_o$. Hence, we proposed that ketamine had a papaverine-like effect on the rat uterus (Calixto *et al.*, 1983) and suggested that the direct relaxant effect of ketamine could be related to the blockade of calcium translocation processes.

In an attempt to clarify the mechanism of relaxation, the inhibitory potency of ketamine was compared with that of papaverine, theophylline and verapamil. The present study indicates that ketamine, like papaverine and theophylline, competitively blocks calcium-induced contractions in the K^+-depolarized uterus of the rat.

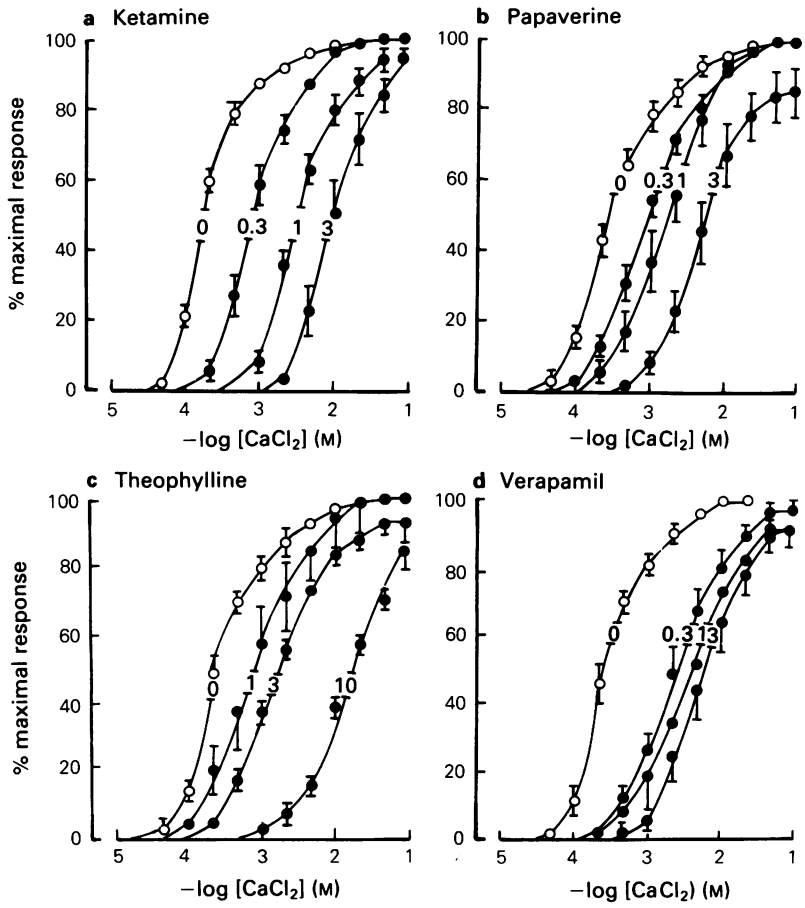

Figure 1 Effect of (a) ketamine ($0.3-3 \times 10^{-3}$ M), (b) papaverine ($0.3-3 \times 10^{-5}$ M), (c) theophylline ($1-10 \times 10^{-4}$ M) and (d) verapamil ($0.3-3 \times 10^{-8}$ M) on the mean cumulative concentration-response curves to $CaCl_2$ obtained in isolated K^+-depolarized rat uteri. (○) Control responses to $CaCl_2$; (●) responses to $CaCl_2$ after pre-incubation with the antagonist, final concentration indicated in each curve. Each point represents the mean of 5 or 6 experiments and the vertical lines the s.e.mean.

Methods

Uterine strips were obtained from adult female Wistar rats (180–250 g) kept in a room, with controlled temperature (22 ± 1°C) and illumination (12 h on and 12 h off). The animals were treated with oestradiol benzoate (0.5 mg kg^{-1}, s.c.) 24 h before the experiments and killed by a blow on the head. Uterine strips (1.5 cm long) free from adhering tissue, were suspended in 10 ml organ baths containing physiological de Jalon solution (composition, mM: NaCl 154, KCl 5.6, $CaCl_2$ 0.3, $MgCl_2$ 1.4, $NaHCO_3$ 1.7 and glucose 5.5) maintained at 30°C and continuously bubbled with air. Isotonic contractions were measured under a resting load of 1 g using a light lever (six fold amplification) writing on a kymograph.

To assess the effects of the Ca^{2+} antagonists on the influx of Ca^{2+} through voltage-sensitive channels (Goodfraind *et al.*, 1968; Weiss, 1981) the strips were bathed for 30–40 min in de Jalon solution and then exposed for 1 h to high-K^+ Ca^{2+}-free depolarizing solution (prepared by replacement of 80 mM NaCl with 80 mM KCl). In general, two cumulative concentration-response curves to $CaCl_2$ (0.04 to 22 mM) were obtained at 60 min intervals in each preparation (Van Rossum, 1963). After obtaining the first curve, washing and after complete relaxation, different concentrations of ketamine (0.3 to 3 mM), papaverine (3 to 30 μM), theophylline (0.1 to 1 mM) or verapamil (3 to 30 nM) were added to the bath and left in contact with the tissue for 20 min. Then, a second cumulative concentration-response curve to $CaCl_2$ was obtained.

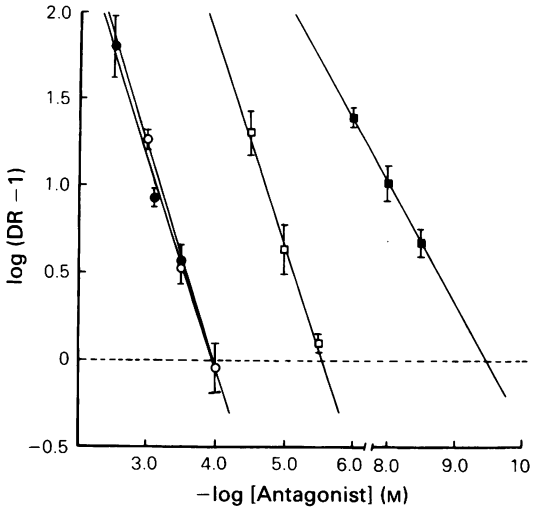

Figure 2 Schild plots for ketamine (○———○); theophylline (●———●); papaverine (□———□); and verapamil (■———■) as antagonists of $CaCl_2$-induced contractions of isolated K^+-depolarized uteri of the rat. The apparent pA_2 values were determined by interpolation using regression analysis. The correlation coefficients obtained were 0.97 ± 0.01; 0.98 ± 0.01; 0.97 ± 0.01 and 0.97 ± 0.01 for ketamine, theophylline, papaverine and verapamil respectively. Each point represents the mean of 5 or 6 experiments and the vertical bars indicate the s.e.means.

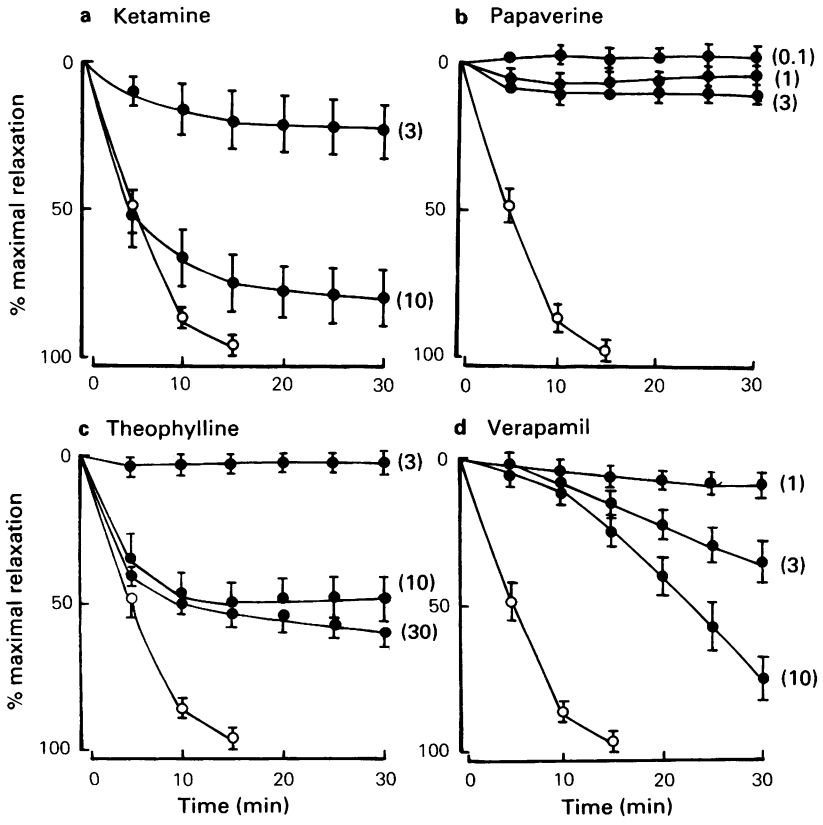

Figure 3 Time courses of the relaxant effects of different concentrations of (a) ketamine (3 and 10×10^{-4} M), (b) papaverine ($0.1-3 \times 10^{-5}$ M), (c) theophylline ($3-30 \times 10^{-4}$ M) and (d) verapamil ($1-10 \times 10^{-8}$ M) compared with those produced by omission of Ca^{2+} from the bathing solution (○———○), on $CaCl_2$ (1 mM)-induced contractions of rat isolated uteri in K^+-depolarizing medium. The concentrations of the compounds in the bath are indicated by the numbers in parentheses. Each point represents the mean of 8 to 10 experiments and the vertical bars indicate the s.e.mean.

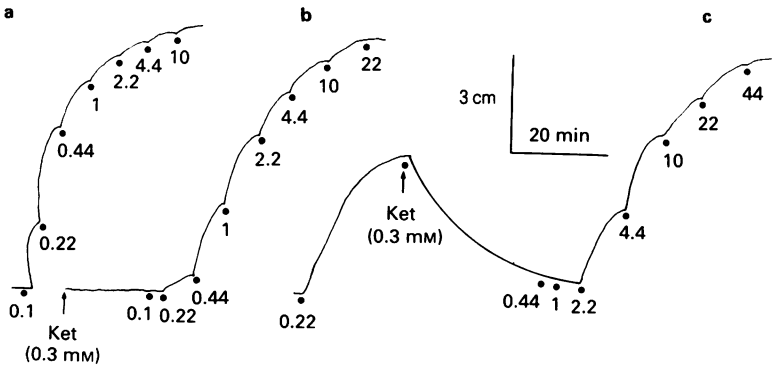

Figure 4 Typical isotonic cumulative concentration-response curves to $CaCl_2$ in high K^+-medium. (a) Control curve, (b) after pre-incubation with ketamine (Ket; 0.3 mM) for 20 min and (c) preparation contracted with a low Ca^{2+} concentration (0.22 mM) for about 10 min, then incubated with ketamine (0.3 mM) for another 20 min. Note that ketamine was more potent in antagonizing the Ca^{2+}-induced contraction, when incubated in the presence of Ca^{2+} (c) than in the absence (b) of Ca^{2+}. Figures refer to final concentration of Ca^{2+} (mM) in the bath.

Each antagonist was tested in separate strips and control experiments were performed using only $CaCl_2$ in the absence of antagonists. The maximal contraction obtained with the first dose-response curve to $CaCl_2$ was taken as 100%, and all contractions calculated as a function of this value. Each preparation was exposed to only one concentration of the antagonist. The apparent pA_2 values for all antagonists were calculated by the method of Arunlakshana & Schild (1959).

Since some Ca^{2+} antagonists may act by blocking the effect of Ca^{2+} within the cell (Spedding, 1983) another set of experiments compared the relaxation induced by these drugs in strips previously contracted with $CaCl_2$ (1 mM) (Hof & Vuarela, 1983). After stabilization of a sustained response (about 10 min) different concentrations of ketamine (0.3 to 1 mM); papaverine (1 to 30 μM); theophylline (0.3 to 3 mM) or verapamil (10 to 100 nM) were added to the bath. The relaxant effect was compared to that obtained when $CaCl_2$ was omitted from the bathing solution.

Another method recently introduced for differentiating Ca^{2+} antagonists compares the potency of these compounds in inhibiting $CaCl_2$-induced contractions, when added to a bath containing a Ca^{2+}-free or low Ca^{2+} depolarizing solution (Spedding, 1982). Therefore, depolarized strips were contracted by a low Ca^{2+} concentration (0.22 mM). When these contractions reached their plateau a fixed concentration of each antagonist was added and incubated for 20 min. Cumulative concentration-response curves to Ca^{2+} were then continued starting with 0.44 mM Ca^{2+} (see Figure 4). The ED_{50} values for these curves were calculated and divided by the ED_{50} of the respective control curves. The quotient between dose-ratios was determined in each case by dividing the dose-ratio obtained in the presence of Ca^{2+} (0.22 mM) by that obtained in Ca^{2+}-free solution.

Statistical analysis

The results are presented, when appropriate, as the mean ± s.e.mean. Statistical significance of differences between the means was assessed using Student's *t* test for unpaired or paired data. *P* values of less than 0.05 were considered to represent significant differences. Schild plots were analysed by linear regression.

Drugs

The following drugs were used: ketamine hydrochloride (Parke-Davis), papaverine hydrochloride, theophylline hydrochloride, oestradiol benzoate (Sigma), and verapamil hydrochloride (Knoll). All drugs were diluted in 0.9% w/v NaCl solution, except oestradiol which was diluted in peanut oil (1 mg ml^{-1}).

Results

Effect of pre-incubation with the antagonists on $CaCl_2$-induced contractions in a depolarizing Ca^{2+}-free medium

Cumulative concentration-response curves in response to $CaCl_2$ (0.04 to 22 mM) on rat uteri immersed in K^+-depolarizing Ca^{2+}-free solution were reproducible at 60 min intervals.

Figure 1 shows the mean cumulative concentration-response curves for $CaCl_2$ alone and in the presence of

different concentrations of ketamine (0.3 to 3 mM), papaverine (3 to 30 μM), theophylline (0.1 to 1 mM) and verapamil (3 to 30 mM). Each drug produced a parallel and concentration-dependent rightward displacement of the dose-response curve to $CaCl_2$ without significantly reducing the maximal response. The Schild plot regression lines for these data (Figure 2) indicate that these drugs, with the exception of verapamil, block $CaCl_2$-induced contractions competitively. The slope of the Schild plot for verapamil differed significantly from unity. The pA_2 values (± s.e.mean) and the mean slope (95% confidence limits) calculated were: ketamine 3.90 ± 0.07, 1.20 (0.90–1.41); theophylline 3.99 ± 0.1, 1.26 (0.97–1.33); papaverine 5.55 ± 0.05, 1.17 (0.99–1.37) and verapamil 9.54 ± 0.24, 0.71 (0.56–0.87). Due to technical limitations it was not possible to test higher concentrations of the antagonists.

Relaxant effects of the antagonists on $CaCl_2$-induced contractions

Tonic contractions elicited by $CaCl_2$ 1 mM corresponded to about 50–80% of the maximal response to the salt and remained stable for more than 30 min.

Figure 3 shows the mean time-response curves of the relaxations, of the $CaCl_2$ (1 mM)-induced contractions of depolarized uteri, induced by ketamine (0.3 to 1 mM), papaverine (1 to 30 μM), theophylline (0.3 to 3 mM), verapamil (10 to 100 nM) or by omission of Ca^{2+}. Ketamine and verapamil produced a concentration-dependent relaxation; however, the $t_{\frac{1}{2}}$ for ketamine was significantly less than that obtained for verapamil (5 and 22 min respectively). In contrast, papaverine was ineffective; and theophylline failed to relax the preparations by more than about 50%. Only ketamine (1 mM) caused a rate of relaxation which approximated to that obtained by washing the preparation with Ca^{2+}-free solution ($t_{\frac{1}{2}}$ = approx. 5 min).

The relaxant effect of the drugs disappeared after washing the preparation with a high K^+ Ca^{2+}-free medium for about 30 60 min, except in the case of verapamil, the effect of which was more persistent, being completely reversed only after washing for 90–120 min.

Effect of pre-incubation with the antagonists on $CaCl_2$-induced contractions in medium containing a low calcium concentration

In preparations contracted by a medium containing a low Ca^{2+} concentration for about 10 min, ketamine (0.3 mM), papaverine (3 μM) and theophylline (0.3 mM), but not verapamil (0.01 μM), behaved differently than in the Ca^{2+}-free experiments. These results are shown in Figures 4 and 5, where the effect of

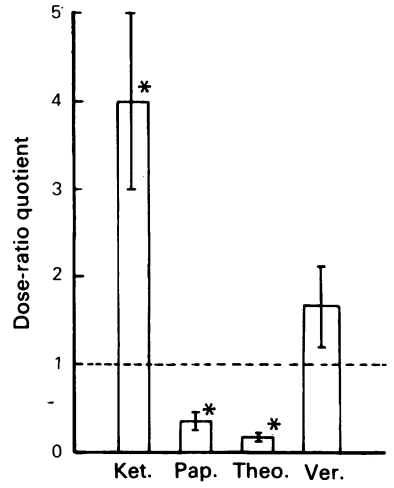

Figure 5 Effect of previous exposure to calcium (0.22 mM) for 20 min on the magnitude of the rightward displacements of the dose-response curves to $CaCl_2$ caused by ketamine (Ket; 0.3 mM), theophylline (Theo; 0.3 mM), papaverine (Pap; 3 μM) and verapamil (Ver; 0.01 μM) in isolated potassium-depolarized uteri of the rat. The dose-ratio quotient refers to the ED_{50} ratio obtained in the presence of Ca^{2+} (0.22 mM) divided by the ED_{50} ratio obtained in Ca^{2+}-free solution. Columns indicate the mean quotient ratio value, and vertical lines s.e.means, from 8 experiments. Asterisks denote ratios significantly different from 1.0 (Student's *t* test).

ketamine and the quotients of the ED_{50} ratios are depicted. It can be seen that in the preparation exposed to a low Ca^{2+} concentration before addition of ketamine, the ED_{50} ratio for calcium was about 4 fold greater than that in preparations not previously exposed to Ca^{2+}. In sharp contrast, in these preparations the ED_{50} values for calcium in the presence of papaverine and theophylline were significantly lower than those obtained in the Ca^{2+}-free experiments. In the presence of verapamil the ED_{50} ratios for calcium did not differ from those obtained in the Ca^{2+}-free medium.

Discussion

Schild analysis of the data showed that inhibition of the uterine contractile response to calcium produced by ketamine, papaverine and theophylline, at least within the range of doses employed, involves a simple competitive mechanism, confirming our previous results (Calixto *et al.*, 1983). In contrast, the antagonism exerted by verapamil is complex since the slope of the Schild regression analysis differed significantly from unity. Assuming that contractions evoked by calcium

chloride in smooth muscle maintained in depolarizing solution are directly related to the influx of Ca^{2+} into the cell (Van Breemen, 1977), we can postulate that ketamine as well as the other compounds tested are presumably interfering competitively with calcium entry through the cell membrane. The relaxant effects of papaverine and theophylline may involve additional mechanisms. These drugs increase the efflux and uptake of Ca^{2+} by intracellular organelles (Thorens & Haeusler, 1979; Takayanagi *et al.*, 1980; Imai & Kitagawa, 1981; Koike & Takayanagi, 1981; Huddart *et al.*, 1983; 1984; Oashi & Takayanagi, 1983) and also inhibit adenosine 3':5'-cyclic monophosphate (cyclic AMP) phosphodiesterase (Weiss & Hait, 1977; Mukai *et al.*, 1981). Furthermore, recent evidence indicates that most of the calcium entry blockers have an additional intracellular site of action, related to an increase of Ca^{2+} efflux or to stimulation of Ca^{2+} uptake (Spedding, 1983; Saida & Van Breemen, 1983; Cohen *et al.*, 1984).

In uteri previously contracted by 1 mM $CaCl_2$, ketamine, in similar concentrations to those that induced rightward displacements of the dose-response curves to $CaCl_2$ of K^+-depolarized preparations in Ca^{2+}-free medium, produced a greater and faster relaxation than the other drugs ($t_{\frac{1}{2}}$ = approx. 5 min). Papaverine was ineffective and theophylline induced a relaxation similar in time-course to, but of smaller magnitude than, that evoked by ketamine, while, verapamil produced a very slow relaxation ($t_{\frac{1}{2}}$ = approx. 22 min). When the preparations were exposed to a low concentration of $CaCl_2$ (0.22 mM) and then pre-incubated with the antagonists, ketamine caused the greatest rightward displacement of the dose-response curve to $CaCl_2$ (Figures 4 and 5); papaverine and theophylline were less potent. The mechanisms and the clinical significance of these phenomena are unclear.

Although inhibition of calcium influx appears to be the major mechanism for the direct relaxant effect of ketamine in the rat uterus, it is likely that this drug may also interfere with calcium availability via an action on intracellular sites, since ketamine can enter the cells with ease (Cohen *et al.*, 1973). Furthermore, ketamine (10^{-4} to 2×10^{-3} M) blocks adrenaline- and noradrenaline-induced contractions in vascular smooth muscle which are dependent on the release of calcium from an intracellular pool (Altura *et al.*, 1980).

In summary, the present findings together with those described previously (Altura & Altura, 1978; Altura *et al.*, 1980; Fukuda *et al.*, 1983; Calixto *et al.*, 1983) suggest that the relaxant effects of ketamine may be due to the blockade of calcium movements across the cell membrane, similar to the calcium entry blockers. However, the fact that ketamine, verapamil, theophylline and papaverine behave differently in previously contracted preparations indicates that they may act on separate sites or in different ways.

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