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The effect of nifedipine and verapamil on KCl-induced rhythmic contractions of guinea pig ureter in vitro

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Summary. Addition of KCl (40 mM) produced rhythmic contractions of guinea-pig ureters in vitro which were unaffected by phentolamine, atropine or tetrodotoxin.
KCl failed to elicit rhythmic contractions of ureters incubated in a Krebs solution with no added Ca^{++}; in these conditions the addition of $CaCl_2$ in concentrations of 1.5 mM, or higher, produced rhythmic contractions whose frequency, but not amplitude, was proportional to $CaCl_2$ concentration in the bathing medium.
EDTA reduced the frequency of KCl-induced rhythmic contractions without affecting their amplitude. Nifedipine and verapamil reduced both the frequency and the amplitude of KCl-induced rhythmic contraction; verapamil was more effective than nifedipine in reducing their amplitude.
Urethane reduced the amplitude without significantly affecting the frequency of KCl-induced rhythmic contractions. An increase in the extracellular Ca^{++} concentration reverted the suppressive effect of all drugs under study. These results suggest that an influx of Ca^{++} from the extracellular space is responsible for the initiation of KCl-induced rhythmic contractions and is involved in the mechanism(s) which regulates their frequency, but that a separate mechanism regulates their amplitude.

Introduction

In the past few years evidence has been provided indicating that the 2 major Ca^{++} entry blockers, nifedipine and verapimil[9,10] exert their effects through different modes of action at cardiac[8,23] and smooth muscle levels[11,13,24,37].
We reported recently that both nifedipine and verapamil reduce the frequency of spontaneous contractions of rat urinary bladder in vivo and that, unlike verapamil, nifedipine only slightly reduced their amplitude[30]. Further studies indicated that spontaneous contractions observed in these experimental conditions are likely to be attributable to a micturition reflex[32,33]. Therefore it appeared worthwhile to determine whether or not differences existed in the smooth muscle relaxant properties of nifedipine and verapamil on isolated smooth muscle from the urinary tract. In this study we report the effects of nifedipine and verapamil on the frequency and amplitude of KCl-induced contractions of guinea pig ureter, a preparation known to exhibit a rhythmic contractile activity[14] when exposed to appropriate K^+ concentrations.
In addition similar experiments were carried out using urethane, a general anesthetic which has been proposed to affect smooth muscle contractility by a mechanism(s) similar to that of organic Ca^{++} blockers[3,30,31,34].

Methods

Male albino guinea pigs, weighing 240–300 g were killed by a blow on the back of the head and exsanguinated. A 2 cm long segment of the right ureter, excluding the region directly connected to the pelvis[14] was removed, desheathed and suspended, under a resting tension of 0.5 g, in a 5 ml organ bath (heated at 37 °C) containing Krebs solution of the following composition (mM): NaCl 119, KCl 4.7, $MgSO_4$ 1.5, KH_2PO_4 1.2, $CaCl_2$, $NaHCO_3$ 25 and glucose 11, which was bubbled with a

mixture of O_2 95% and CO_2 5%. In experiments to elucidate the potential effects of extracellular Ca^{++} deprivation on KCl-induced contractions, a Ca^{++} free Krebs solution (with or without EDTA) was used; this was obtained by preparing a Krebs solution with no added Ca^{++}. Although this medium might well contain minute amounts of endogenous Ca^{++} as impurities, it will be referred thereafter as Ca^{++}-free Krebs solution. Mechanical responses were recorded by means of a MARB 79 T1 isometric transducer. After a 30 min equilibration period contractions were elicited by the addition of KCl 40 mM. Since hypertonic solutions are known to cause contraction in smooth muscle preparations in vitro, control experiments[4,22] were performed with glucose 80 mM.

In a first series of experiments we examined the effect of increasing concentrations of test substances on the frequency and amplitude of the rhythmic contractions produced by KCl 40 mM. Drugs were added in a cumulative manner, the next concentration being administered when the effects of the preceding one had reached a steady state. Total volume administered did not exceed 150 µl.

To study the effects of extracellular Ca^{++} concentration on the rhythmic contractions produced by KCl 40 mM, 2 Ca^{++} deprivation procedures were employed:

Procedure A. after a 30-min equilibration period in normal Krebs the ureters were incubated for 3–4 min in a Ca^{++}-free Krebs solution with repetitive washings during this period and then challenged with KCl 40 mM.

Procedure B. after a 30-min equilibration period in normal Krebs the ureters were placed for 30 min in a Ca^{++}-free Krebs solution containing EDTA 0.77 mM with repetitive washings every 5 min. Then the preparations were exposed for 30 min to a Ca^{++}-free Krebs solution without EDTA with repetitive washings every 5 min; then KCl 40 mM was added, which failed to produce contractile responses. 2 min later, a concentration response curve to Ca^{++} was constructed by the cumulative addition of $CaCl_2$ to the organ bath, the next concentration being added when the effects of the preceding one had reached a steady state. In some experiments when rhythmic contractions induced by KCl 40 mM had been suppressed by the test substances the effect of increasing the extracellular Ca^{++} concentration to 7.5 mM was determined. Since artificial buffers commonly used to prevent precipitation of divalent cations in in vitro experiments have been shown to affect Ca^{++} exchangeability[43], as well as smooth muscle contraction[2] no attempt was made to avoid Ca^{++} precipitation, and, consequently, these experiments have been evaluated only from a qualitative point of view.

Statistical analysis

Results are expressed as mean ± SE. Statistical analysis was performed by means of Student's t-test for paired or unpaired data, as appropriate. Regression analysis was performed by means of the least squares method.

Drugs

The following drugs were used: verapamil HCl (Isoptin, Knoll) nifedipine (Bayer), ethylenediamminotetracetic acid disodium salt (EDTA) (BDH), phentolamine mesylate (Regitin, Ciba), atropine HCl (Serva), urethane (Serva), tetrodotoxin (Sankyo) and procaine HCl (Gianni).

A 1 mM solution of nifedipine in absolute ethanol was prepared, from which a 1 µM dilution in Krebs was made just before the beginning of the concentration response curve. Care was taken to avoid exposure of nifedipine solutions to light. The concentrations of drugs and chemicals are expressed as final molar concentrations in the organ bath.

Results

Effects of high K^+, phentolamine and atropine

An example of KCl-induced rhythmic concentrations of guinea pig ureter is shown in figure 1. The mean values of frequency and amplitude were 4.8 ± 0.08 contractions/min (range 0.8–9) and 377.7 ± 20.1 mg (range 62–681) (n = 64) respectively. Steady state values of frequency and amplitude are reached within 10 min from

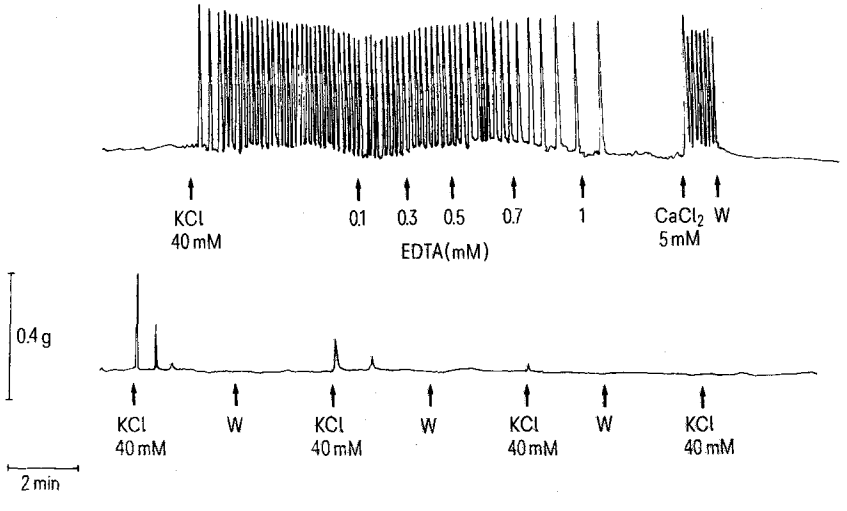

Figure 1. *Upper panel.* Typical tracing showing the effect of KCl (40 mM) on isolated guinea-pig ureter. Note that KCl induces a series of rhythmic contractions without a concomitant rise in resting tension. At steady state EDTA (0.1–1 mM) is cumulatively added until a suppression of KCl-induced contractions is obtained. $CaCl_2$ 5 mM is then added (in addition to the 2.5 mM $CaCl_2$ already present in Krebs solution) and restores the rhythmic activity; W = washing out.

Lower panel. Typical tracing showing the effects of KCl (40 mM) on isolated guinea-pig ureter after the Ca^{++} deprivation procedure A (see the methods for details). Washing out (W) with Ca^{++} free Krebs solution and repetition of exposure to KCl leads to an exhaustion of KCl contractile effects.

the exposure to KCl and remain constant for at least 20–30 min, a period of time sufficient for studying the effect of substances. No significant correlation exists between frequency and amplitude of KCl-induced contractions of guinea pig ureter in control conditions ($r = 0.147$, $n = 64$, not shown). Removal of KCl with normal Krebs produced an immediate disappearance of rhythmic contractions. Glucose 80 mM had no contractile effect on guinea pig ureter in normal Krebs medium. Neither phentolamine (3 μM, $n = 6$), atropine (3 μM, $n = 6$) nor tetrodotoxin (0.5 μM, $n = 5$) had a significant inhibitory effect on KCl-induced contractions at steady state.

Effects of calcium deprivation and readmission

Procedure A. Following a brief exposure to a Ca^{++}-free medium, KCl induced 1–4 phasic contractions which rapidly declined in amplitude and subsided. Washing out KCl with Ca^{++}-free Krebs solution and re-exposure to KCl resulted in contractions of lower amplitude and number. Repetition of this procedure led to a complete failure to respond to KCl (fig. 1).
In none of the 8 preparations did KCl induce regular rhythmic contractions.
Procedure B. In none of the 10 preparations did KCl induce any type of contraction. Addition of increasing quantities of $CaCl_2$ led to rhythmic contractions in 5 out of 10 preparations at an extracellular Ca^{++} concentration of 1.5 mM and in 10 out of 10 preparations at an extracellular Ca^{++} concentration of 2.0 mM. While the frequency of contractions was dependent upon extracellular Ca^{++} concentration even above 2.5 mM, amplitude was nearly maximal at 1.5 mM (fig. 2).

Effect of procaine on KCl-induced rhythmic contractions

Procaine (1 mM) produced a significant ($p < 0.01$) increase in both frequency (from 5.8 ± 1.5 to 8.8 ± 1.4 contractions/min, $n = 7$) and amplitude ($32.3 \pm 4.0\%$ increase) of KCl-induced rhythmic contractions. In 4 out of 7 preparations the excitatory effects of procaine (1 mM) were characterized by the appearance of phasic contractions which declined slowly to the resting tone values with several phasic contractions of lower amplitude superimposed during the decline. Procaine (3 mM) produced a further enhancement in frequency of KCl-induced rhythmic contractions (from 5.8 ± 1.5 to 19.6 ± 1.6, contractions/min, $p < 0.001$), but a marked decrease in amplitude ($68.2 \pm 3.6\%$, $n = 4$) and suppression of contractions in 3 out of 7 preparations (fig. 3). Procaine (5 mM) suppressed contractions in the remaining 4 preparations. Procaine-induced suppression of KCl-induced rhythmic contractions was characterized by the appearance of a slight contracture (30–100 mg) above the resting level. Increased extracellular Ca^{++} concentrations (up to a total of 7.5 mM) reverted the suppressive effect of procaine (fig. 3).

Effect of EDTA on KCl-induced rhythmic contractions

EDTA (0.3–1 mM) produced a concentration-dependent decrease in frequency of KCl-induced rhythmic contractions without any significant effect on amplitude (fig. 1, 4A). A significant correlation exists between the concentration of EDTA required to suppress KCl-induced contractions and the initial rate of discharge of each preparation ($r = 0.818$, $n = 13$, $p < 0.01$) (fig. 5). Raising the extracellular Ca^{++} concentration up to a total of 7.5 mM led to a complete recovery in both frequency and amplitude (fig. 1).

Effect of nifedipine, verapamil and urethane on KCl induced rhythmic contractions

Nifedipine (1–40 nM, $n = 13$) (fig. 4B) and verapamil (0.1–1 μM, $n = 13$) (fig. 4C) produced a concentration-

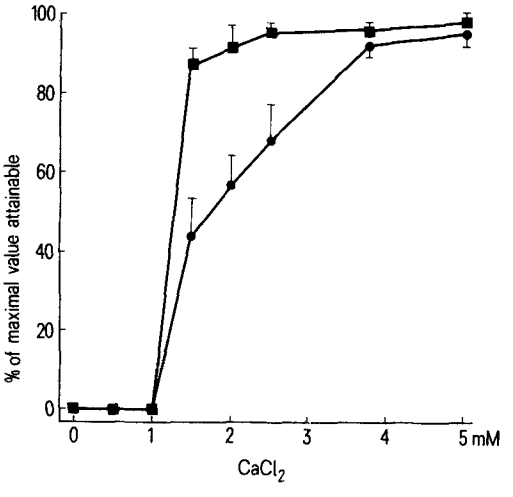

Figure 2. Effect of increasing quantities of $CaCl_2$ on frequency (●) and amplitude (■) of rhythmic contractions produced in guinea pig ureters exposed to KCl 40 mM after the Ca^{++} deprivation procedure B (see the methods for details. Each value ($n = 10$, mean ± SE) is expressed as a percentage of the maximal frequency and amplitude attainable in each preparation.

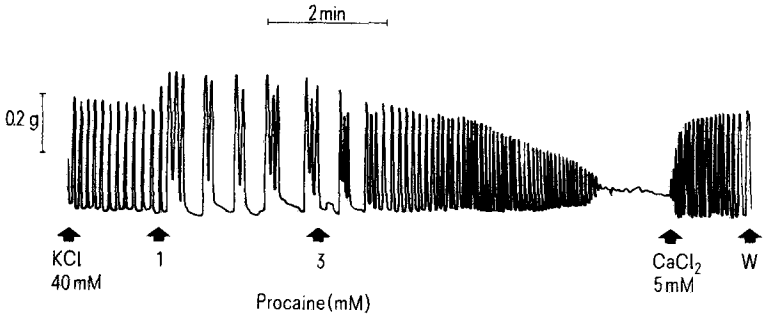

Figure 3. Typical tracing showing the effects of procaine (1–3 mM) on KCl-induced rhythmic contractions of guinea pig ureter. See the text for details.

dependent decrease in frequency and amplitude of KCl-induced rhythmic contractions. The inhibition of amplitude produced by verapamil (46.5 ± 4.3%) was significantly greater ($p < 0.001$) than that produced by nifedipine (19.3 ± 2.7%). Urethane (3–30 mM, n = 13) (fig. 4D) produced a significant concentration-dependent decrease in amplitude of KCl-induced rhythmic contractions. Only at 20 mM concentration did urethane inhibit significantly their frequency. Urethane, in concentrations lower than 20 mM reduced the frequency of KCl-induced rhythmic contractions in 8 out of the 13 preparations, augmented it in 3 and had no effect in 2. A significant correlation exists between the concentration of nifedipine ($r = 0.7624$, $n = 13$, $p < 0.01$), verapamil ($r = 0.9188$, $n = 13$, $p < 0.01$) and urethane ($r = 0.7145$, $n = 13$, $p < 0.01$) required to suppress KCl-induced rhythmic contractions of guinea pig ureter, and the initial frequency of contraction of each preparation (fig. 5). Increasing extracellular Ca^{++} concentration up to a total of 7.5 mM reversed the suppressive effect of verapamil, nifedipine and urethane.

Discussion

Exposure of smooth muscle preparations to high K^+ depolarizing solutions is thought to produce: a) enhancement of the translocation of Ca^{++} across the membrane through voltage sensitive Ca^{++} channels[16, 36, 47] and b) release of neurotransmitter(s) from the autonomic nerve endings present in the smooth muscle tissue[6, 12, 38]. This ultimately leads to a contraction which can be phasic or tonic or of both types depending upon the degree of K^+-induced depolarization and the preparation under study[5]. It has been shown that high K^+ induces rhythmic phasic contractions of guinea pig ureters without an appreciable rise in their resting tension[14, 15] and this behavior has been explained in terms of a K^+ induced cyclic release of neurotransmitter(s)[39]. However, the failure of either atropine, phentolamine or tetrodotoxin to alter KCl contractile effects indicates that, in our experimental conditions, neurotransmitter(s) release could hardly be held responsible for the maintenance of rhythmic contractions of guinea pig ureter[45].

Whether or not neurotransmitter(s) release participates in their genesis, our results indicate that KCl-induced rhythmic contractions of guinea pig ureter are markedly dependent upon the presence of Ca^{++} in the bathing medium. This is in agreement with previous findings which similarly indicate that no contractile activity can be elicited in guinea pig ureters exposed to a high K^+ medium free of Ca^{++}[19, 42, 45]. Previous findings have indicated that ureteral smooth muscle has a poor development of the sarcoplasmic reticulum[21] which is thought to be the major intracellular storing system for releasable Ca^{++}[5, 41]. In the light of this, the observation that procaine, in a concentration which is fully effective in antagonizing Ca^{++} release from intracellular storage sites[17, 35] does not inhibit the amplitude of KCl-induced rhythmic contractions is evidence against the participation of intracellular Ca^{++} stores in this phenomenon.

It has been proposed that, in the guinea pig ureter, K^+ induces phasic contractions by mobilizing a loosely-bound Ca^{++} pool, while tonic contractions are sustained by an influx of Ca^{++} from the extracellular space[1, 7]. Our results agree well with this hypothesis; in fact the observation that KCl is able to initiate phasic contractions of guinea pig ureter exposed for a short (procedure A) but not a long (procedure B) period to a Ca^{++}-free medium could be interpreted as an indication that phasic contractions depends upon the mobilization of a loosely-bound Ca^{++} from the store. In addition, the failure of KCl to generate a rhythm after Ca^{++} deprivation (procedure A) and the rapid exhaustion of its contractile effects produced by washing with Ca^{++}-free medium in-

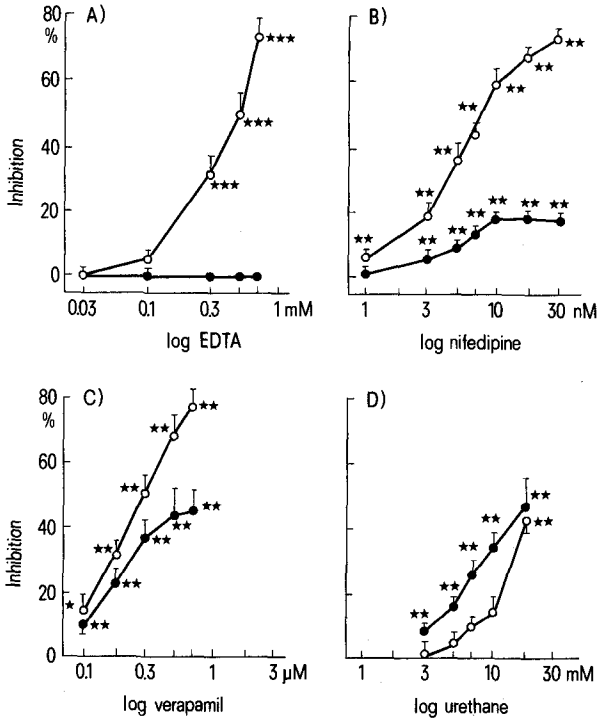

Figure 4. Effect of EDTA (A), nifedipine (B) verapamil (C) and urethane (D) on frequency (○) and amplitude (●) of contractions produced by exposure to hypertonic KCl (40 mM) of isolated guinea pig ureters (n = 13); *p < 0.05; **p < 0.02; ***p < 0.01.

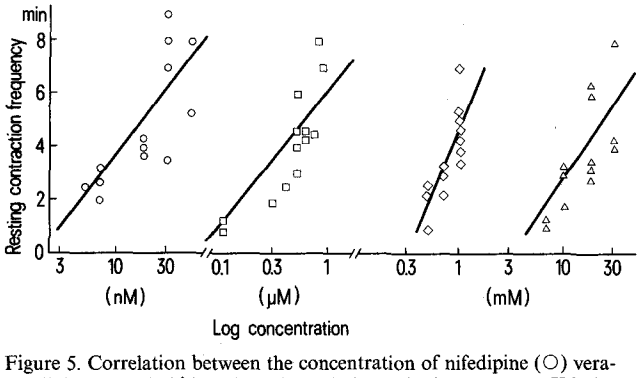

Figure 5. Correlation between the concentration of nifedipine (○) verapamil (□) EDTA (◇) and urethane (△) required to suppress KCl-induced rhythmic contraction in any given guinea pig ureter and its initial frequency of contraction. N = 13 for each drug, r is 0.7624, 0.9188, 0.8180, and 0.7145 for nifedipine, verapamil, EDTA and urethane respectively and p is < 0.01 for each drug.

dicate that, for a regular rhythm to be established, the putative store which binds Ca^{++} loosely needs to be replenished almost immediately with extracellular Ca^{++}. The effects of KCl observed after procedure A could be ascribed to an incomplete removal of extracellular Ca^{++}. However, the results obtained with procedure B do not support this hypothesis; in fact, the results of experiments with Ca^{++} readmission following Ca^{++} deprivation (procedure B) indicate the existence, for each ureteral preparation, of a critical extracellular Ca^{++} concentration, sufficient to sustain a regular rhythm, below which no contraction is elicited by KCl. Since KCl induced some phasic contraction after procedure A but failed to generate a rhythm, an incomplete removal of extracellular Ca^{++} could hardly explain these results.

Results obtained with the Ca^{++} deprivation and readmission (procedure B) indicate that KCl-induced mobilization of Ca^{++} involves qualitative differences in the processes regulating frequency and amplitude of the rhythmic contractions. In fact, while frequency is related in a concentration-dependent manner to extracellular Ca^{++} concentration, amplitude follows an all or none type of response. From these observations it is tempting to speculate that: a) a small direct influx of extracellular Ca^{++} through channels activated by KCl depolarization is responsible for the generation of the phasic contractions and b) this triggers the intracellular release of a loosely (membrane) bound Ca^{++} pool forming the bulk of activator Ca^{++} which regulates the amplitude of contraction. Results obtained using EDTA support this hypothesis. In fact, increasing concentrations of EDTA (which can be assumed to produce a progressive decrease in extracellular Ca^{++} concentration) progressively reduced the frequency of KCl-induced rhythmic contractions without affecting their amplitude. In this regard it is worth mentioning that, although the precise ionic currents which are responsible for the action potential of guinea pig ureter, in both resting conditions and during K^+ stimulation[14, 27, 40, 44, 45] are far from being elucidated, an inward movement of Ca^{++} appears to be involved in its generation and the external concentration of Ca^{++} is of importance for the initial spike as well as the shape and the duration of the plateau of the potential[21, 29].

Alternatively, since an EDTA sensitive, loosely membrane-bound Ca^{++} pool has been described as occurring in several smooth muscle preparations[47] the hypothesis could be put forward that 2 distinct loosely-bound Ca^{++} pools are responsible for the frequency and amplitude of KCl-induced rhythmic contractions of guinea pig ureter. Quite obviously the interpretation of functional data presented in this study is highly speculative. Further studies are required to determine the validity of the proposed mechanisms regulating frequency and amplitude of KCl-induced rhythmic contractions of guinea pig ureter.

Our results indicate that both verapamil and nifedipine interfere with the mechanism which is responsible for the generation of KCl-induced rhythmic contraction and regulates their frequency; in addition, verapamil is more effective than nifedipine in inhibiting the mechanism which regulates the amplitude of contraction.

In a previous paper we reported similar quantitative differences between verapamil and nifedipine in affecting frequency and amplitude of spontaneous rhythmic contractions of rat urinary bladder[30] which could be attributed to a repetitive micturition reflex[32, 33]. Since Ca^{++} entry blockers are known to have only minimal effects on neurotransmitter release from nerve endings[20], the differential effects of these drugs on the micturition reflex in vivo could be ascribed to differences in their action on urinary bladder smooth muscle. This hypothesis is substantiated by the present findings on guinea pig ureter in vitro.

Procaine had a composite effect on KCl-induced rhythmic contractions of guinea pig ureter, i.e. enhancement at low and suppression at high concentrations. These observations are in keeping with those of Washizu[46] who reported that procaine, in low concentrations, increased the duration of the action potential and the number of oscillations on its plateau. This was associated with an initial increase in contractile amplitude followed by inactivity when higher concentrations of procaine were applied[46]. Since the return of the membrane potential of guinea pig ureteral cells to the resting level after an action potential appears to be related to an increase in the permeability of the cell membrane to K^+[14] it is likely that the excitatory effect of a low concentration of procaine is attributable to its inhibitory effect on K^+ conductance[25, 26]. On the other hand, the suppressive effect of higher concentrations of procaine on KCl-induced rhythmic contractions of guinea pig ureter could be ascribed to a decreased Ca^{++} permeability of the cell membrane[16, 18, 46]. This is substantiated by the observation that increased extracellular Ca^{++} concentration reverted procaine-induced suppression.

Our findings on guinea pig ureter support the hypothesis that the smooth-muscle relaxant properties of urethane are attributable to its interference with Ca^{++} availability[3, 31, 34]. However, its mechanism of action appears to be different from that of nifedipine or verapamil since urethane, while reducing the amplitude, does not affect the frequency of KCl-induced contractions. Amplitude or ureteral contractions is reduced by urethane in concentrations which are of the same order of magnitude as those required to reduce the amplitude (without any effect on frequency) of the spontaneous contractions of rat portal vein[3] but are about $1/10$ of the concentrations required to antagonize Ca^{++}-induced contractions in KCl depolarized preparations[3, 31, 34]. This raises the possibility that, depending upon the preparation under study and/or the concentrations used, urethane might interfere with: a) mobilization of loosely-bound Ca^{++} from the store (at concentrations equal to or lower than 10 mM); b) mobilization of tightly-bound Ca^{++} from the store (at concentrations between 10 and 50 mM)[34] and, c) transmembrane Ca^{++} fluxes through voltage sensitive[3, 31, 34] and receptor operated Ca^{++} channels (at concentrations equal to or higher than 50 mM)[34].

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