

## Effects of Ketamine on Contractile Responses in Vascular Smooth Muscle

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*This study was designed to determine the effects of ketamine on contractions induced by norepinephrine (NE), K<sup>+</sup> or histamine (Hist) and on agonist-induced calcium mobilization, in rabbit thoracic aorta with or without endothelium. Contractile responses to NE, K<sup>+</sup> or Hist were markedly attenuated by prior exposure to ketamine. Subsequent addition of ketamine to the rabbit aorta undergoing an isometric contraction induced by NE, K<sup>+</sup> or Hist also decreased the contractile responses in a calcium ion concentration-dependent manner. Preincubation with ketamine produced a concentration-dependent inhibition of contractile responses elicited by the addition of calcium ion (1.6mM) to a Ca<sup>2+</sup>-free depolarizing solution. However, the phasic contraction produced by NE with 2mM lanthanum pretreatment, which is release of intracellular calcium, was also inhibited by ketamine. Moreover, the tonic contraction produced by NE after depletion of the agonist-releasable pool of intracellular calcium, which is thought to be due to calcium influx, was depressed by ketamine. These data suggest that ketamine relaxes NE-contracted rings of rabbit thoracic aorta by decreasing calcium entry and by producing an extracellular calcium-independent relaxant effect.*

**Key Words:** Ketamine, vascular smooth muscle contractility, Ca<sup>2+</sup> mobilization, rabbit thoracic aorta

Ketamine is an intravenous anesthetic agent which produces dissociative anesthesia. It is related to phenylcyclohexylamine compounds. Clinical and experimental studies with ketamine have shown that cardiovascular stimulation often occurs during ketamine anesthesia. The cardiovascular responses to ketamine in man include tachycardia, increased cardiac output, a pressor response, increased cardiac index, increased stroke volume index and increased pulmonary arterial pressure (Domino *et al.* 1965; McCarthy *et al.* 1965; Tweed *et al.* 1972; Ivankovich *et al.* 1974; McGrath *et al.* 1975; Clanachan *et al.* 1976; Idvall *et al.* 1979). On the other hand, other investigators using the heart muscle or cardiac preparations have documented the opposite effects of ketamine on myocardial contractility (Dowdy and Kaya 1968; Traber *et al.* 1968; Goldberg *et al.* 1970; Schwartz and Hor-

witz 1975; Urthaler *et al.* 1976). These discrepancies regarding the hemodynamic effects of ketamine may be due to differences in experimental setup, dosage employed and/or the animal species used (McCarty *et al.* 1965; Dowdy and Kaya 1968; Traber and Wilson 1969; McGrath *et al.* 1975).

In the present investigation, the effects of ketamine on the vascular smooth muscle contraction induced by various vasoactive agents were examined in the isolated rabbit thoracic aorta with or without endothelium.

The results suggest that the mechanism by which ketamine induces endothelium-independent relaxation may be explained by a specific effect of ketamine on a portion of cellular calcium located at the superficial membrane site, decrease of calcium entry and/or production of an extracellular calcium-independent relaxant effect.

### MATERIALS AND METHODS

#### Preparation of Rabbit Aorta Ring and Tension Recording

Locally supplied white rabbits weighing 2 to 3 kg of either sex were killed by stunning and exsanguina-

Received April 17, 1990

Accepted July 23, 1990

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This study was supported by the Faculty Research Fund, 1988, Yonsei University College of Medicine.

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tion. The descending thoracic aorta was removed carefully to protect the endothelial lining, placed in a petri dish filled with Krebs solution (mM: NaCl, 118; KCl, 4.8;  $\text{CaCl}_2$ , 2.5;  $\text{MgSO}_4$ , 1.2;  $\text{KH}_2\text{PO}_4$ , 1.2;  $\text{NaHCO}_3$ , 24; glucose, 11; disodium EDTA, 0.03, pH 7.4), cleared of adhering fat and connective tissues and was then cut into 2 to 3mm long rings. In some experiments, endothelial cells were removed from aortic rings by gently rubbing the intimal surface with a wooden stick for 30 to 60 sec (Furchgott and Zawadzki 1980a, b). Successful removal of endothelial cells from aortic rings was confirmed by the inability of acetylcholine (ACh) to induce relaxation, and in some experiments, by histological examination of the intimal surface using a silver staining technique (Poole *et al.* 1958). The rings were mounted under 2g of resting tension on L-shaped stainless-steel hooks in 20ml muscle chambers and were bathed in Krebs solution ( $37^\circ\text{C}$ , gassed with 95%  $\text{O}_2$  and 5%  $\text{CO}_2$ ). The tension was measured isometrically using a Grass FTO3 force displacement transducer and was displayed on a model 7 Grass polygraph. The tissue was allowed to equilibrate for 120 minutes before experiments were begun. Each preparation was examined to find out if  $10^{-6}\text{M}$  ACh induced an almost complete relaxation of a  $10^{-7}\text{M}$

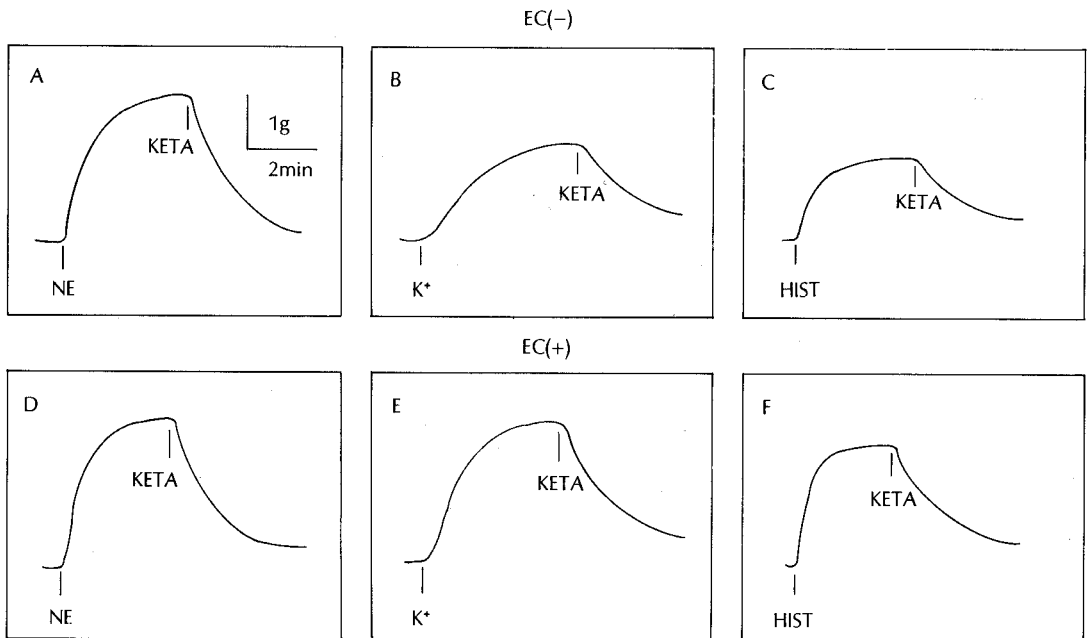
norepinephrine (NE)-induced contraction in order to determine the functional integrity of the endothelium. In the aortic rings from which the endothelium had been rubbed off, the  $10^{-6}\text{M}$  ACh-induced relaxation was more than 80% of the NE-induced contraction. Ketamine was added 5 minutes prior to and during sustained contraction induced by vasoactive agents. A  $0\text{-Ca}^{++}$  and high  $\text{K}^+$  solution (depolarizing) was also employed and was identical to the Krebs solution except that  $\text{CaCl}_2$  was omitted and the KCl concentration was increased to 80mM.

### Drugs

Vasoactive agents employed in this study were potassium chloride ( $\text{K}^+$ ), l-norepinephrine bitartrate (NE), and histamine hydrochloride (Hist). These agents as well as ketamine hydrochloride (ketamine) were pipetted from concentrated stock solutions directly into the bathing media to give the final concentration desired.

### Data Presentation and Analysis

Results were expressed as the mean  $\pm$  SE and com-



**Fig. 1.** Representative tracings showing transient relaxation produced by 4.0mM ketamine when added to a ring of rabbit thoracic aorta with [EC(+)] or without [EC(-)] endothelium precontracted by  $10^{-7}\text{M}$  norepinephrine (NE, A), 40mM potassium ( $\text{K}^+$ , B) or  $9\mu\text{M}$  histamine (Hist, C).

parisons were made using Student's t-test. A probability of 0.05 or less was considered significant.

## RESULTS

### Vasodilating effects of ketamine on vasoactive agents-induced contraction

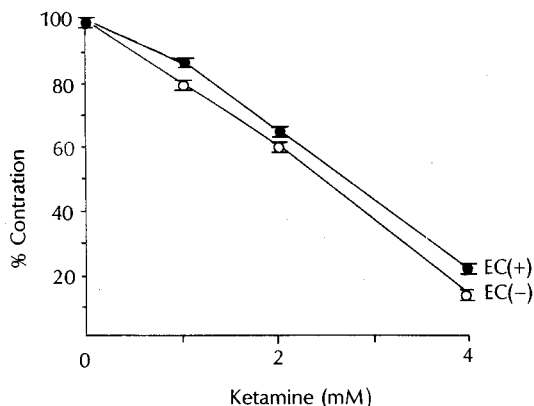
Phasic and tonic contractions were induced by NE ( $10^{-7}$ M),  $K^+$  (40mM) and Hist ( $9\mu$ M) in rabbit thoracic aortic rings. Recordings of typical patterns of dilator responses induced by ketamine in aortic rings with and without endothelium are shown in Fig. 1 A, B, C, D, E and F, respectively. In eight preparations, ketamine inhibited the contractile responses of aortic rings with or without endothelium in a dose-dependent manner (Fig. 2). This result suggests that the ketamine-induced relaxation is endothelium independent.

### Effects of ketamine on isometric contractions induced by norepinephrine

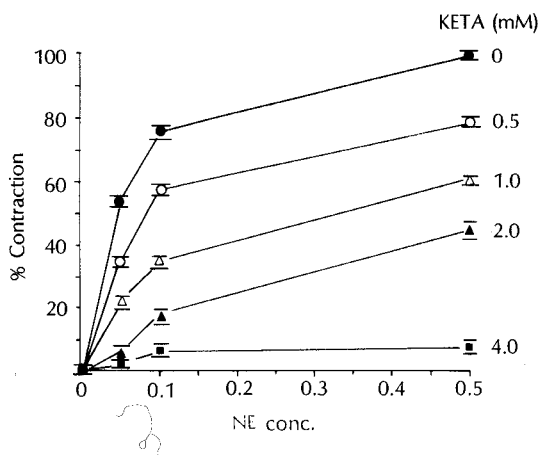
The inhibitory effects of ketamine were obtained by examining the degree of inhibition of contractile responses to NE after prior exposure to ketamine (0.5, 1.0, 2.0 and 4.0mM). Thirty minutes after control dose-responses for NE were obtained, aortic rings were exposed to the desired concentration of ketamine for 5 minutes prior to obtaining another dose-response curve for NE. Alterations in contractile responses after exposure to ketamine were calculated by dividing the maximum height of the experimental contractions at each NE concentration by the maximum contraction height (100%) obtained with  $0.5\mu$ M NE (control contraction) in the same aortic rings. This is illustrated graphically in Fig. 3. It can be seen that 4.0mM ketamine inhibited the NE-induced contractile responses to the greatest degree and that the degree of inhibition is related to the concentration of ketamine employed.

### Effects of different calcium concentrations on the inhibitory effect of ketamine on contractile responses induced by norepinephrine, histamine or $K^+$

To determine if the inhibitory actions of ketamine are  $Ca^{++}$  dependent, tension responses elicited in aortic rings with NE,  $K^+$  and Hist were determined in bathing media containing 0.05, 0.5 and 1.5mM  $Ca^{++}$ . The aortic rings were equilibrated for 30 minutes in the Krebs solution and then were rinsed twice with a solution containing the desired calcium concentration. They were incubated in this solution for 20



**Fig. 2.** Dose-response curves showing the effects of ketamine on the relaxation of a ring of rabbit thoracic aorta with [EC(+)] or without [EC(-)] endothelium precontracted by  $10^{-7}$ M norepinephrine (NE). Each data point represents mean  $\pm$  SE of 8 experiments.

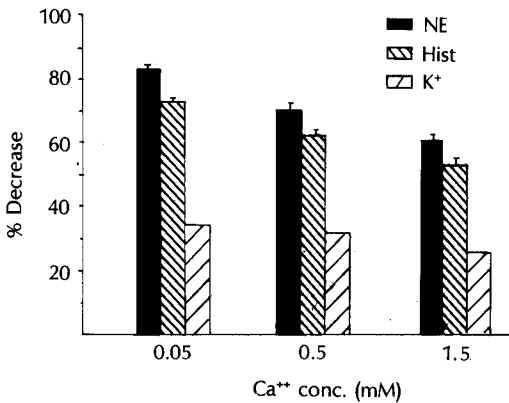


**Fig. 3.** Effects of ketamine on isometric contractions induced by norepinephrine (NE) in isolated aortic rings without endothelium.

The results are expressed as a percentage of the maximum control contraction obtained with the highest concentration of norepinephrine (NE) in each experiment. Each value is the mean  $\pm$  SE of 8 experiments.

\*  $p < 0.05$

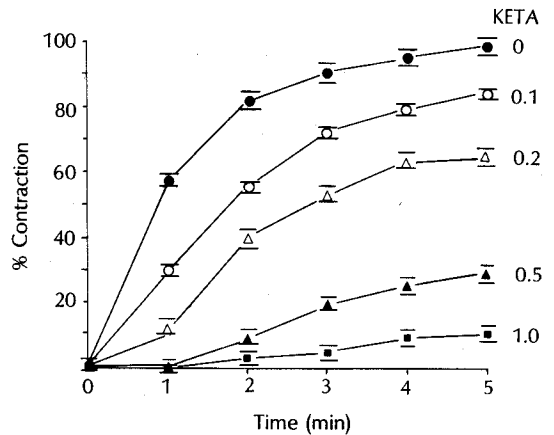
minutes prior to exposure to vasoactive agents. Then, after obtaining control contractile responses for 5 min., 4.0mM ketamine was added to the bathing solution



**Fig. 4.** Effect of different calcium concentrations on the inhibitory effect of ketamine on tension responses induced by norepinephrine (NE), potassium (K<sup>+</sup>) or histamine (Hist).

Tension responses were obtained for 5 minutes and 4.0mM ketamine was then added to the bath. Results are expressed as a percentage of the maximum height obtained prior to the addition of ketamine. Each value is the mean  $\pm$  S.E. of 8 experiments.

\*  $p < 0.05$



**Fig. 5.** Effects of preincubation with ketamine on contractile responses produced in aortic rings by addition of Ca<sup>++</sup> (1.6mM) to a Ca<sup>++</sup> free K<sup>+</sup>-depolarizing (80mM) solution.

Results are expressed as a percentage of the maximum control response obtained 5 minutes after addition of 1.6mM Ca<sup>++</sup>. Control value responses are mean  $\pm$  S.E. of 8 experiments. Ketamine was added 5 minutes prior to Ca<sup>++</sup>.

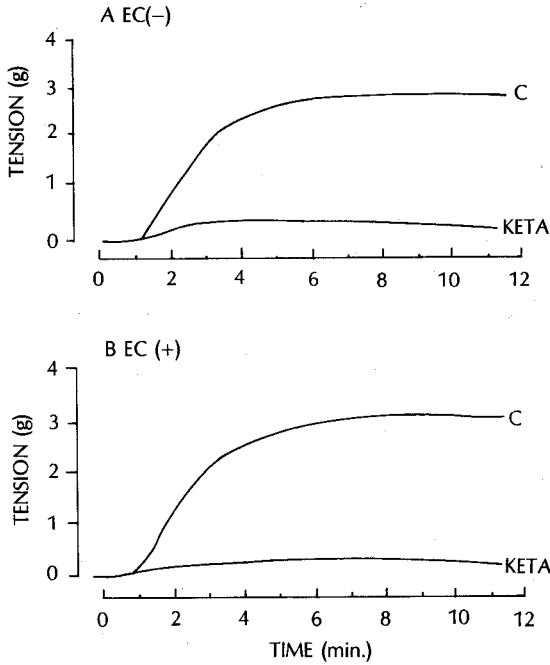
\*  $p < 0.05$

in the presence of the vasoactive agents. Contractile responses induced by NE, Hist, and K<sup>+</sup> were decreased by the subsequent addition of ketamine. Furthermore, increasing the Ca<sup>++</sup> concentration of the bathing solution from 0.05mM to 0.5mM and 1.5mM attenuated the inhibitory effects of 4.0mM ketamine (Fig. 4).

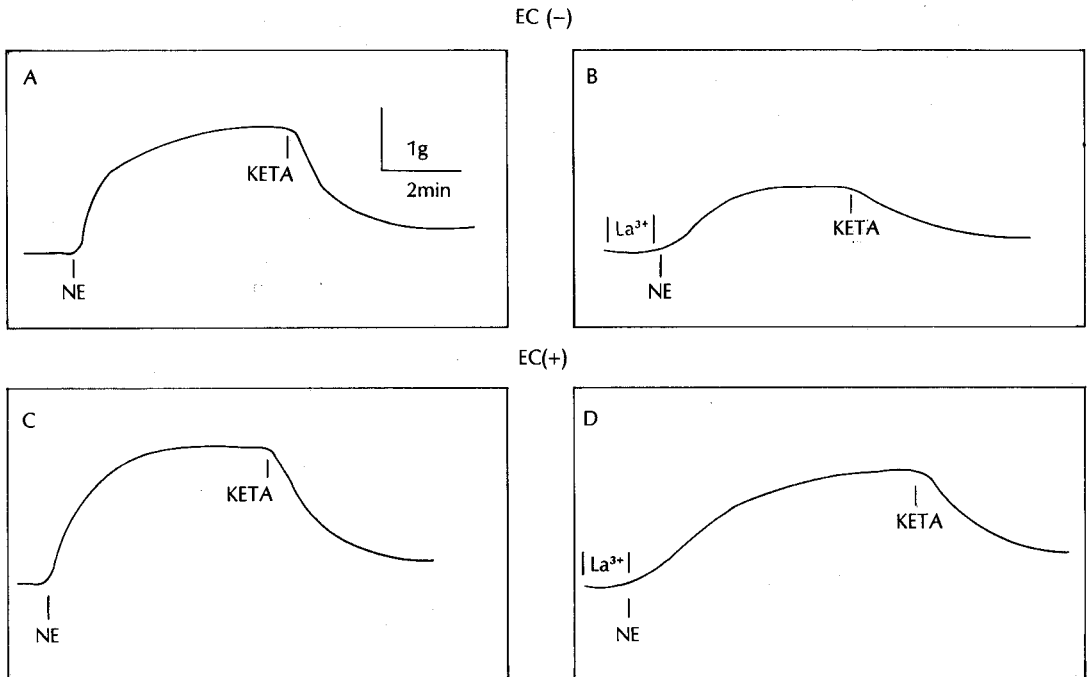
#### Effects on calcium mobilized by vasoactive agents

In order to examine the effects of ketamine on contractile responses produced by addition of Ca<sup>++</sup> to a Ca<sup>++</sup>-free high K<sup>+</sup> (80mM, depolarizing) solution, further experiments were conducted with depolarized aortic rings. Addition of Ca<sup>++</sup> to normal Krebs solution or to Ca<sup>++</sup>-free depolarizing solution does not elicit a contractile responses in aortic rings. However, Ca<sup>++</sup> produces a contractile response when added to a Ca<sup>++</sup>-free solution in which the K<sup>+</sup> concentration has been increased sufficiently to depolarize the cell membrane (Godfraid and Kaba 1969; Brecht and Gebert 1969; Carrier and Jurevics 1973). After stabilization of aortic rings in normal solution, the bathing media were replaced several times with 0 Ca<sup>++</sup> solution. After 30

minutes, the 0 Ca<sup>++</sup> solution was replaced with a 0 Ca<sup>++</sup> depolarizing solution for 10 minutes. A 5 minute contractile response to Ca<sup>++</sup> (1.6mM) was obtained with aortic rings before and after exposure to 1.0mM ketamine. Values were expressed as a percentage of the maximum tension obtained from the first control response after 5 minutes exposure to 1.6mM Ca<sup>++</sup>. As seen in Fig. 5, preincubation with ketamine for 5 minutes produced a concentration-dependent attenuation of the contractile response elicited by Ca<sup>++</sup> in aortic rings. In addition, the inhibitory effect of ketamine on Ca<sup>++</sup>-induced contractile responses is readily reversible. Contractions of aortic rings produced by NE are caused by both influx of extracellular calcium and release of intracellular calcium (Van Breeman *et al.* 1972; Deth and Van Breeman 1974). A test was devised to determine whether ketamine could inhibit the force generated by calcium influx. Aortic rings were contracted for 10 minutes by NE in Ca<sup>++</sup>-free Krebs solution containing 2mM ethylene glycol-bis-( $\beta$ -aminoethyl ether) N,N'-tetraacetic acid (EGTA). A subsequent contraction could not be pro-



**Fig. 6.** Effects of ketamine on the  $10^{-7}M$  NE contraction produced solely by calcium influx. Rings of rabbit thoracic aorta with [EC(+)] or without [EC(-)] endothelium were contracted by NE in a calcium-free, 2mM EGTA-containing solution for 10 minutes. A subsequent contraction could only be produced by NE if 1.5mM calcium was present. This contraction (C), which is thought to be due to calcium influx, was inhibited when ketamine was added at the same time as calcium (KETA).



**Fig. 7.** The relaxation produced by 4.0mM ketamine when added to a ring of rabbit thoracic aorta with or without endothelium precontracted by  $10^{-7}M$  NE in the presence of nonspecific calcium antagonist lanthanum ( $La^{3+}$ ). Lanthanum was added 10 minutes before NE. Ketamine was added when a maximum NE contraction was achieved.

duced unless calcium was added to the solution. This contraction was presumably caused by an increase in cytosolic calcium brought about solely by calcium influx (Van Breeman *et al.* 1972; Deth and Van Breeman 1974). The contraction produced by NE stimulated calcium influx was greatly attenuated by 4.0mM ketamine (Fig. 6). To determine whether ketamine can also relax the NE-induced contraction that can be produced when influx of extracellular calcium is prevented, ketamine was added to aortic rings at the peak of the contraction produced by NE in the presence of 2mM lanthanum ( $\text{La}^{3+}$ ). Ketamine caused an inhibition of the NE-generated force (Fig. 7). The inhibition by ketamine of the force generated by NE when calcium influx was blocked by  $\text{La}^{3+}$  suggests that ketamine may cause an increase in calcium sequestration or efflux.

## DISCUSSION

In the isolated rabbit aorta with or without endothelium, ketamine attenuated the contractile responses to NE,  $\text{K}^+$  and Hist in a dose-dependent manner (Figs. 1 and 2). This result suggests that endothelial cells are not involved in the ketamine-induced relaxation.

It has been documented that  $\text{Ca}^{2+}$  is essential for activation of the contractile mechanism in various smooth muscle systems (Diamond 1973; Greenberg *et al.* 1973; Hudgins and Weiss 1968; Somlyo and Somlyo 1968; Somlyo and Somlyo 1970). In vascular smooth muscle, how  $\text{Ca}^{2+}$  is taken up, distributed, bound to cellular constituents, and subsequently utilized may play an important role in determining the manner in which the tissue responds mechanically to vasoactive agents (Somlyo and Somlyo 1968; Somlyo and Somlyo 1970). In the present study, contractile responses produced by high  $\text{K}^+$ , Hist and NE, were attenuated by ketamine to the greatest extent when the aortic rings were incubated in a low  $\text{Ca}^{2+}$  bathing solution. At the lowest  $\text{Ca}^{2+}$  concentration (0.05mM  $\text{Ca}^{2+}$ ), ketamine was most effective as an inhibitor of tension responses induced by NE, Hist, and  $\text{K}^+$  (Fig. 4). This action of ketamine, which is dependent upon the level of  $\text{Ca}^{2+}$  in bathing solution, could be attributed to an inhibition of  $\text{Ca}^{2+}$  uptake.

Goodman and Weiss (1971), in studying the effect of  $\text{Ca}^{2+}$  found that the contractile responses to NE, Hist and  $\text{K}^+$  in isolated aortic strips could be divided into rapid (initial) and slow (maintained) components. The influx of extracellular calcium is thought to be important for initiation of  $\text{K}^+$  induced responses (Briggs 1962)

and for maintenance of tension responses elicited by NE or Hist. Conversely, sequestered calcium may be of importance for the initial component of the contractions induced by NE or Hist (Hinke 1965; Hudgins and Weiss 1968) as well as for the slow component of the  $\text{K}^+$ -induced contraction (Goodman *et al.* 1972). The experiments summarized in Fig. 4 reinforce this conclusion and suggest that ketamine may inhibit the uptake of  $\text{Ca}^{2+}$  by affecting binding of  $\text{Ca}^{2+}$  to the superficial membrane site.

Additional experiments were conducted with aortic rings in order to examine the nature of the  $\text{Ca}^{2+}$  dependence of the effect of ketamine. An examination of contractile responses produced in aortic rings by addition of  $\text{Ca}^{2+}$  to a  $\text{Ca}^{2+}$ -free depolarizing solution provided additional evidence for a superficial site of action of ketamine in this preparation. Under these conditions, contractile events would depend, initially, upon the movement of added  $\text{Ca}^{2+}$  across the depolarized smooth muscle cell membrane. Preincubation with ketamine consistently inhibited contractions elicited by addition of  $\text{Ca}^{2+}$ ; however, even with a higher concentration of ketamine, addition of ketamine to  $\text{Ca}^{2+}$ -contracted aortic rings produced no discernible effects on the developed tension. Therefore, the ketamine appears to selectively inhibit the uptake, binding and/or availability of a superficial  $\text{Ca}^{2+}$  fraction in the vascular smooth muscle.

Cytosolic calcium levels in vascular smooth muscle are regulated by calcium channel activity, membrane-bound calcium pumps, and intracellular sequestering mechanisms (Van Breeman *et al.* 1980). Since the level of cytosolic calcium directly determines the extent of force generated by the vascular smooth muscle (Filo *et al.* 1965; Chatterjee and Murphy 1983), ketamine-induced relaxation may result from alteration of agonist-induced calcium mobilization. When the ability of ketamine to relax the NE-induced contraction as well as the sustained contraction was examined, it was found that ketamine (4.0mM) significantly attenuated, but did not eliminate NE-induced contraction produced after depletion of the agonist-releasable intracellular calcium pool. This reinforces the contention that one action of ketamine is to block calcium influx.

In order to determine the effect of ketamine on the extracellular calcium-independent contraction produced by NE, ketamine was added to vascular rings when the force produced by NE in the presence of 2mM  $\text{La}^{3+}$  was maximal, and any relaxation produced was compared to the force from the maximum level. Ketamine produced a rapid and strong relaxa-

tion. These data suggest that ketamine can relax the NE-contracted rabbit aorta through a mechanism that is distinct from calcium influx blockade in the vascular smooth muscle, implying that ketamine can accelerate the removal of calcium from the cytosol of vascular smooth muscle cells by causing an increase in kinetics or the affinity for calcium at certain points involved in calcium sequestration and extrusion.

In summary, ketamine significantly attenuated the contractile responses generated by NE, Hist and  $K^+$ . The ability of ketamine to attenuate NE, Hist and  $K^+$ -induced vascular tone was independent of the endothelium. Calcium influx blockade by ketamine could not, however, completely explain the ability of ketamine to relax the precontracted rabbit aorta, since the relaxation occurred in the presence of the calcium influx blocker,  $La^{3+}$ . These data suggest that ketamine relaxes NE-contracted rings of rabbit thoracic aorta by decreasing calcium entry and by producing an extracellular calcium-independent relaxant effect. Further work on the effect of ketamine on the uptake, storage and/or utilization of  $Ca^{++}$  may help to gain an insight into the mechanisms by which ketamine modulates the vascular smooth muscle tone.

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