The Effects of Ketamine on Spiral-cut Strips of Rabbit Aorta

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The effects of ketamine on spiral-cut strips of rabbit aorta in the uncontracted state and when contracted to half-maximal with phenylephrine or with histamine were studied. Ketamine did not produce contraction in concentrations between $10^{-9}$ and $10^{-3}$ M, indicating a lack of direct alpha-adrenergic receptor-stimulating activity. Ketamine relaxed phenylephrine- and histamine-contracted strips to equivalent extents and at approximately the same concentrations. However, these concentrations were much greater than concentrations of phentolamine and diphenhydramine needed to produce relaxation under the same conditions, suggesting that the action of ketamine differs from the actions of alpha-adrenergic blocking agents and antihistamines. Concentrations needed to relax the phenylephrine-contracted strip were greater than those of isoproterenol and were not influenced by pretreatment with propranolol, suggesting a lack of beta-adrenergic receptor-stimulating activity. The high concentrations of ketamine needed to produce relaxation were similar to those of local anesthetics, especially lidocaine, suggesting that its mechanism of action on aortic smooth muscle is similar to that of local anesthetics. (Key words: Anesthetics, intravenous: ketamine; Arteries: ketamine; Histamine; Sympathetic nervous system: alpha-adrenergic receptors; Sympathetic nervous system: beta-adrenergic receptors; Sympathetic nervous system: sympatholytic agents: propranolol; Sympathetic nervous system: sympatholytic agents: phentolamine; Sympathetic nervous system: sympathomimetic agents: isoproterenol; Sympathetic nervous system: sympathomimetic agents: phenylephrine.)

The blood-pressure response to ketamine is biphasic in animals and in man.1–3 The depressor phase occurs first, is of short duration, and is not always observed following low doses. The depressor phase is attributed in part to a direct negative inotropic effect on the myocardium.4 The pressor response which follows is thought to result at least in part from desensitization of the afferent fibers of the baroreceptor reflex, leading to an uninhibited vasomotor center and thus sympathetic stimulation.4 In dogs the pressor phase is attenuated by alpha-adrenergic blocking agents, ganglionic-blocking agents, and complete epidural anesthesia.7–9 The pressor response is predominantly and is associated with increased cardiac output and elevated plasma levels of catecholamines.5–10

Observed changes in systemic vascular resistance induced by ketamine have been inconsistent. Virtue et al.5 found no change in systemic resistance, while Kreuscher and Gauch11 found a 25 per cent decrease in man. Tweed et al. found a variable change of ± 25 per cent in patients pretreated with diazepam whose hearts were paced during cardiac catheterization. Changes in systemic resistance were time-dependent, with an increase within the first 3 minutes after administration of ketamine, whereas the maximal cardiac index occurred 4–10 minutes after injection.12 The delayed increase in cardiac index could be explained by an initial negative inotropic effect with recovery after sympathetic stimulation.

Traber et al.13 found no change in the systemic vascular resistance of dogs which received ketamine, 5 mg/kg, and a decrease after 10 mg/kg. In isolated perfused limbs of dogs, ketamine produced slight vasodilation, at high concentrations only.14

The present investigation was undertaken to define more precisely the direct vascular response to ketamine by studying its effect on the smooth muscle of the rabbit aorta.

Methods and Materials

Spiral-cut aortic strips of the rabbit were prepared as described by Furchgott.15–18 Rabbits (2–3 kg) were stunned by a blow on the head. The descending thoracic aorta was isolated and placed in Krebs physiologic solution. The adventitial surfaces were cleaned, and spiral strips 3–4 mm wide and 4 cm long (unstretched) were prepared and mounted under

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4-g tension in a muscle chamber containing 150 ml of the physiologic solution. The solution was aerated vigorously with 95 per cent O₂-5 per cent CO₂ and maintained at pH 7.35-7.45 and a constant temperature of 38 C. Changes in isometric contractile tension were recorded with a force-displacement transducer (Grass FT-03) and recording polygraph (Grass Model 7). Each preparation was allowed to equilibrate for two hours prior to study. The ketamine preparation was in the form of the hydrochloride salt, made isotonic with sodium chloride. Each ml contained 10 mg ketamine base and 1:10,000 benzethonium chloride as a preservative. In previous experiments it was found that concentrations of benzethonium chloride present commercially with ketamine from $10^{-7}$ to $10^{-3}$ M concentrations did not have significant effects on isometric contraction of the left atrial strip of the rabbit.\$ However, this preservative was not examined for effect on the aortic smooth muscle.

Concentrations of phenylephrine and histamine which cause contraction amounting to half of the maximum contraction under the above conditions were determined from a concentration-response study (fig. 1). The ability of ketamine to contract the aortic strip was examined in concentrations ranging from $10^{-9}$ to $10^{-3}$ M.

The effects of ketamine on aortic strips contracted by histamine and by phenylephrine were examined in the following manner. Experimental and control aortic strips were brought to a state of half-maximal contraction by addition of phenylephrine, $1.5 \times 10^{-7}$ M, or histamine, $2.3 \times 10^{-8}$ M. The constant state of contraction was reached approximately 20 minutes after addition of phenylephrine and 40 minutes after histamine and lasted about an hour. During the second hour, there was a slight decrease in tension. The experiments were performed during the first half hours after reaching the constant states of contraction. All drugs were added to the bath in volumes of less than 0.5 ml of saline solution and the concentrations expressed as the negative logs of the molar concentrations. A control strip was employed and received only the contracting drug during each experiment. When the control strip lost more than 10 per cent of the initial tension by the end of the experiment, the data from the other strips were discarded. The following studies were performed.

**Experiment 1**

The effects of ketamine on the phenylephrine-contracted strip with and without pretreatment for 30 minutes with propranolol, $10^{-6}$ M, were determined. This was compared with the effect of isoproterenol, known in low concentrations to relax the contracted strip by its beta-adrenergic receptor-stimulating action.\$\textsuperscript{16}

**Experiment 2**

The effect of ketamine on the phenylephrine-contracted strip was compared with the effect of phentolamine, a compound known to relax the phenylephrine-contracted strip by its alpha-adrenergic receptor-blocking action.\$\textsuperscript{17}

**Experiment 3**

The effect of ketamine on the histamine-contracted strip was compared with the effect of diphenhydramine, which is known to relax histamine-contracted smooth muscle by its antihistaminic action.\$\textsuperscript{17,18}

**Experiment 4**

The concentrations of ketamine needed to relax phenylephrine- and histamine-contracted strips were compared with those of lidocaine, procaine, and quinidine, which are thought to relax the contracted strip by a nonspecific mechanism.

**Results**

Ketamine in concentrations ranging from $10^{-8}$ to $10^{-3}$ M did not produce contraction of the aortic strip. The concentration of phenylephrine needed to produce half-maximal contraction of the strip was $1.5 \times 10^{-7}$ M and that for histamine, $2.3 \times 10^{-8}$ M. These data are illustrated in figure 1.

**Comparison of the Effects of Ketamine and Isoproterenol on Phenylephrine-Contracted Aortic Strip**

Isoproterenol in a concentration of $10^{-9}$ M did not produce an effect, but $10^{-8}$ to $10^{-6}$ M

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\textsuperscript{1} Ketaject, supplied by Bristol Research Laboratories.

\textsuperscript{5} Dowdy, E.C., Yamanaka, I.: Effects of commercial preservatives commonly used in intravenous anesthetics on the isometric contraction of the left atrial strip of the rabbit, unpublished data.
produced significant relaxation of the phenylephrine-contracted aortic strip (Fig. 2). Maximal relaxation, 47 ± 2 per cent from the initial contracted state, occurred with 10^{-6} M. As the concentration was increased, relaxation gave way to contraction. 10^{-5} M produced contraction 10.9 ± 2 per cent greater than the initial state. When the contracted strips were pretreated with propranolol, 10^{-6} M, for 30 minutes, the maximal relaxation produced by isoproterenol was only 11.4 ± 3 per cent. Relaxation produced by isoproterenol, 10^{-6} M, alone was significantly different from that produced when the strips were pretreated with propranolol (P < 0.001).

In contrast to isoproterenol, ketamine produced relaxation only in concentrations of 3 × 10^{-5} M or more (Fig. 2). Pretreatment with propranolol had no significant effect on the relaxation produced by ketamine.

**Comparison of the Effects of Phenolamine, Diphenhydramine, and Ketamine on Phenylephrine-Contracted Aortic Strip**

(Fig. 3)

The effective concentrations of phenolamine, diphenhydramine, and ketamine that relaxed the phenylephrine-contracted aortic strip were definitely different. Phenolamine produced relaxation with concentrations between 10^{-9} and 10^{-7} M, diphenhydramine between 10^{-7} and 10^{-4} M, and ketamine between 3 × 10^{-5} and 10^{-3} M.

**Comparison of the Effects of Phenolamine, Diphenhydramine, and Ketamine on Histamine-Contracted Aortic Strip**

(Fig. 3)

Phenolamine, diphenhydramine, and ketamine also relaxed the histamine- contracted strip, each in a different manner. Phenolamine produced relaxation with concentrations between 10^{-7} and 3 × 10^{-5} M, diphenhydramine between 3 × 10^{-5} and 10^{-6} M, and ketamine between 3 × 10^{-5} and 10^{-3} M. The concentrations of ketamine needed to relax the phenylephrine- and histamine-contracted strips were 1.5 × 10^{-5} M. Comparison of the effects of propranolol, 10^{-8} M, on relaxation produced by ketamine and by isoproterenol. Each curve represents the mean (± SE) of seven experiments. Statistical significances of the differences between mean percentages of relaxation with and without propranolol were determined by Student's t test. With molar concentrations of isoproterenol, 10^{-8}, P < 0.01, 10^{-7}, P < 0.001, and 10^{-6}, P < 0.001. There was no significant difference between extents of relaxation produced by ketamine with and without pretreatment with propranolol.
FIG. 3. Effects of ketamine, phentolamine, and diphenhydramine on the aortic strip contracted by histamine, 2.3 x 10^-8 M, and by phenylephrine, 1.5 x 10^-7 M. Each curve represents the mean (± SE) of seven experiments. The concentrations of ketamine needed to produce relaxation were similar regardless of the agonist employed and were quite different from those of the specific antagonists phentolamine and diphenhydramine.

FIG. 4. Effects of quinidine, lidocaine, procaine, and ketamine on the aortic strip contracted with phenylephrine, 1.5 x 10^-7 M. The percentage relaxation (ordinate) at a given concentration has been plotted as a function of the negative logarithm of the concentration of the designated drug (abscissa). Each curve is constructed from the mean (± SE) derived from seven experiments.

FIG. 5. Effects of quinidine, lidocaine, procaine, and ketamine on the aortic strip contracted by histamine, 2.3 x 10^-8 M. The percentage relaxation (ordinate) at a given concentration has been plotted as a function of the negative logarithm of the concentration of the designated drug (abscissa). Each curve is constructed from the mean (± SE) derived from seven experiments.
Fig. 6. Concentrations of various drugs needed to produce 50 per cent relaxation of aortic strips brought to half-maximal contraction by pretreatment with phentolamine, 1.5 x 10^{-7} M, and histamine, 2.3 x 10^{-4} M. Each point represents the mean of seven experiments. Note that those drugs to the left of the line have alpha-adrenergic receptor-blocking activity and those to the right of the line, histamine receptor-blocking activity. Ketamine, lidocaine, and procaine are very near the line.

contracted strips to equivalent extents were similar.

Comparison of the Effects of Quinidine, Procaine, Lidocaine, and Ketamine on Phenylephrine-contracted Aortic Strip (Fig. 4)

Quinidine relaxed the phenylephrine-contracted strip in concentrations between 10^{-7} and 10^{-4} M and procaine between 10^{-3} and 8 x 10^{-4} M. The effective concentrations of ketamine and lidocaine were similar; lidocaine was active at 10^{-3} and 8 x 10^{-4} M and ketamine at 3 x 10^{-3} and 10^{-2} M. Some of the differences and similarities can be shown by comparison of the percentages of relaxation produced by 10^{-5} M concentrations of these drugs, which were: quinidine, 97.7 ± 1.4; procaine, 6.2 ± 1.0; lidocaine, -1.2 ± 0.8; ketamine, 2.2 ± 0.6. Another comparison may be seen in table 1, where the negative logarithms of the molar concentrations of these agents needed to produce 50 per cent depression of the aortic strip brought to half-maximal contraction by pretreatment with phentolamine, 1.5 x 10^{-7} M, are listed. It can be seen that ketamine and the local anesthetics are similar, while quinidine is different.

Discussion

Phenylephrine and histamine contract the isolated aortic strip of the rabbit by acting on different specific receptors. In the present study, ketamine did not contract the strip in concentrations ranging from 10^{-9} to 10^{-2} M, indicating that ketamine does not stimulate the alpha-adrenergic receptors or histamine receptors of the aortic strip. The ability of ketamine to relax an aortic strip brought to a moderate tone by the previous addition of phenylephrine is unlike that of isoproterenol, because a much higher concentration of ketamine is needed to relax this preparation and the relaxation is not antagonized by propranolol. These experiments suggest that ketamine does not stimulate beta-adrenergic receptors directly.

Certain alpha-adrenergic blocking agents such as phentolamine relax the contracted aortic strip, not only as antagonists of the alpha-adrenergic stimulating drugs, but also as antagonists of contraction induced by histamine or KCl. Diphenhydramine is known antagonist of the effect of histamine on the aortic strip. It also relaxes the epinephrine-contracted strip, but the dissociation constant

| Table 1. Negative Logarithms of Molar Concentrations Needed for 50 Per Cent Depression of Aortic Strips Brought to Half-maximal Contraction by Pretreatment with Phenylephrine, 1.5 x 10^{-7} M, and Histamine, 2.3 x 10^{-4} M* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Phenylephrine-contracted Strip | Histamine-contracted Strip |
| Phenolamine     | 7.57 ± 0.03     | 5.17 ± 0.07     |
| Diphenhydramine| 4.78 ± 0.08     | 7.65 ± 0.04     |
| Quinidine       | 6.05 ± 0.01     | 4.00 ± 0.02     |
| Procaine        | 3.99 ± 0.05     | 4.19 ± 0.01     |
| Lidocaine       | 3.39 ± 0.07     | 3.30 ± 0.01     |
| Ketamine        | 3.55 ± 0.03     | 3.19 ± 0.04     |

* Data are means ± SEM of seven experiments.
differs from that of the histamine-contracted strip. The concentration of ketamine necessary to relax aortic strips previously contracted with phenylephrine and histamine were far greater than concentrations of phenolamine and diphenhydramine (fig. 3); however, the same concentrations of ketamine relaxed both phenylephrine- and histamine-contracted strips to equivalent extents. It would, therefore, seem that the mechanism of relaxation by ketamine differs from those of alpha-adrenergic blocking agents and antihistamines.

Quinidine is thought to exercise a mild, but specific, depressant effect on the alpha-adrenergic receptor. The similarity of concentrations of quinidine and phenolamine needed to relax the phenylephrine-contracted strip and the difference between concentrations of quinidine and diphenhydramine needed to relax the histamine-contracted strip are illustrated in figure 6. Concentrations of ketamine needed to relax strips contracted by both agonists were more similar to those of the local anesthetics than to those of quinidine. Specifically, ketamine was more similar to lidocaine than to procaine (fig. 6).

These data indicate that ketamine does not stimulate beta-adrenergic receptors and neither stimulates nor inhibits alpha-adrenergic receptors of the rabbit aortic strip. Since concentrations of ketamine needed to produce relaxation are similar to those of local anesthetics, perhaps the mechanism is similar. These data do not predict how systemic vascular resistance will be altered by therapeutic doses of ketamine, since the relaxation observed occurred only at high concentration of ketamine. However, they do suggest that any change which occurs will not be the result of a direct effect on the adrenergic or histamine receptors of arterial smooth muscle.

References
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