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EFFECTS OF KETAMINE ON VASCULAR SMOOTH MUSCLE FUNCTION

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1 *In vitro* studies were undertaken on rat aortic strips and portal vein segments to determine whether or not the amine-type anaesthetic, ketamine, can exert direct actions on vascular smooth muscle.

2 Ketamine was found to inhibit development of spontaneous mechanical activity and lower basal tension. This action took place with ketamine concentrations found in anaesthetic plasma concentrations, i.e., 1×10^{-5} to 2×10^{-4} M.

3 Ketamine (10^{-5} to 10^{-3} M) dose-dependently attenuated contractions induced by adrenaline, noradrenaline, angiotensin II, vasopressin and KCl. These inhibitory actions were observed with ketamine added either before or after the induced contractions.

4 Ca^{2+}-induced contractions of K^+-depolarized aortae and portal veins were also attenuated, dose-dependently, by ketamine.

5 In contrast to the above inhibitory actions, ketamine (2×10^{-6} to 1×10^{-4} M) was found to potentiate specifically 5-hydroxytryptamine(5-HT)-induced contractions of both aortic and venous smooth muscle. However, this was only observed if ketamine was added after 5-HT had initiated a contractile response.

6 All of the inhibitory, as well as 5-HT-potentiating, effects were completely, and almost immediately, reversed upon washing out the anaesthetic from the organ baths.

7 A variety of pharmacological antagonists failed to mimic or affect the inhibitory effects induced by ketamine.

8 These data suggest that rat plasma concentrations of ketamine commonly associated with induction of surgical anaesthesia can induce, directly, relaxation and contractile potentiation of vascular muscle.

9 These diverse findings may aid in explaining the well-known biphasic pressor actions of ketamine.

Introduction

In 1965, a new intravenous amine-type agent, ketamine hydrochloride (Domino, Chodoff & Corssen, 1965; McCarthy, Chen, Kaump & Ensor, 1965), was introduced as a rapidly acting non-barbiturate general anaesthetic which, supposedly, would be free from respiratory and cardiovascular side-effects. Among other side-effects (Dundee & Wyant, 1974; Hamilton, 1976), ketamine has been shown to produce marked rises in blood pressure, cardiac output, heart rate and peripheral blood flow in man and some other mammals, including the rat (Corsen & Domino, 1966; Virtue, Alanis, Mari, Lafargue, Vogel & Metcalf, 1967; Traber, Wilson & Priano, 1968; Chang, Chan & Ganendran, 1969; Dundee & Wyant, 1974; Hug, 1979).

Ketamine has also been shown to produce biphasic blood-pressure responses in man, rats, rabbits and dogs; the depressor phase usually appears first and is short-lived (Domino *et al.*, 1965; McCarthy *et al.*, 1965; Dowdy & Kaya, 1966; Virtue *et al.*, 1967). More recently, it has been suggested that ketamine can also produce peripheral vasoconstriction in certain vascular beds (Traber, Wilson & Priano, 1971; Johnstone, 1976). In contrast to these reports, others have demonstrated that anaesthetic doses of ketamine can result in profound hypotension in certain species, including monkeys, rabbits, and rats (Clanachan & McGrath, 1976; Clanachan, McGrath & MacKenzie, 1976; McGrath & McKenzie, 1977; Ochsner, 1977). Although ketamine is thought to exert some direct cardiac effects (Dundee & Wyant, 1974; Adams, Parker & Mathew 1977; Horowitz, 1977), as well as a

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cocaine-like effect on vascular smooth muscle (Nedergaard, 1973), it is not clear as to whether this general anaesthetic can exert direct actions on peripheral blood vessels (Dundee & Wyant, 1974; Johnstone, 1976).

The present studies were therefore undertaken to determine whether ketamine can exert direct actions on rat arterial and venous smooth muscle. The results presented herein do indeed indicate that concentrations of ketamine used to induce surgical anaesthesia can induce, directly, both potent depressant and contractile-potentiating effects on rat arterial and venous smooth muscle.

Methods

Preparation of aortic strips and portal veins

Thoracic aortae and portal veins were obtained from male rats (Wistar strain, 300 to 425 g) after they had been killed by guillotining. Only male rats were used in these studies since sex and oestrogenic hormones, are known to influence vascular reactivity (Altura, 1972; Altura & Altura, 1977) and the anaesthetic action of ketamine in rats (Livingston & Waterman, 1977). The aortae were cut helically into vascular strips (1.3 to 1.5 mm wide by 25 mm long) and set up isometrically, *in vitro*, under a resting tension of 1.5 g, essentially as described previously (Altura and Altura, 1975). Ten-millimeter segments of portal veins were also arranged isometrically, *in vitro*, and set up under a resting tension of 500 mg (Altura & Altura, 1975). The vascular preparations were equilibrated for 2 h in muscle chambers containing Krebs-Ringer bicarbonate solution, the composition of which was (mmol/l): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgCl_2$ 1.2, $NaHCO_3$ 25.0 and glucose 10.0. The Krebs-Ringer bicarbonate solution was oxygenated continuously with a 95% O_2 and 5% CO_2 mixture and kept at 37°C (pH 7.4 to 7.5). The loading tensions were maintained and periodically adjusted throughout the experiments. The incubation media were routinely changed every 10 to 15 min. The recording equipment was identical to that described previously (Altura & Altura, 1970).

Types of experiments

After the 2 h incubation period, the following experiments were carried out on tissues from different animals.

Vascular strips were exposed to Krebs-Ringer bicarbonate containing various concentrations of ketamine (10^{-6} to 2.1×10^{-3} M) for 5 to 120 min periods to determine whether ketamine hydrochloride affected base-line tension and/or development of spontaneous mechanical activity.

In other experiments, aortae and portal veins were exposed to noradrenaline bitartarate, adrenaline hydrochloride, angiotensin II amide, vasopressin ([8-lysine]-vasopressin), 5-hydroxytryptamine creatinine sulphate (5-HT), or KCl before and after exposure to different concentrations of ketamine (10^{-6} to 2.1×10^{-3} M; 5 to 30 min preincubations). In these experiments single doses of agonists were used in equi-potent concentrations (e.g., ED_{40}-ED_{60}, depending upon agonist) as well as complete cumulative concentration-effect curves. The results for these experiments are expressed as a percentage of the maximal control agonist-induced contractile responses and in developed isometric tension (mg). In addition, various doses of ketamine were added after the establishment of single dose agonist-induced contractile responses.

In certain experiments, the vascular preparations were exposed to various pharmacological antagonists 20 to 30 min before the addition of ketamine to determine whether ketamine-induced responses are affected by α-adrenoceptor blockade (phentolamine, 0.1 to 0.5 μg/ml), β-adrenoceptor blockade (propranolol hydrochloride 0.5 μg/ml), 5-hydroxytryptamine receptor blockade (methysergide maleate, 0.25 μg/ml), cholinoceptor blockade (atropine sulphate, 0.5 μg/ml), histamine receptor blockade (diphenhydramine hydrochloride, 0.5 μg/ml) or a prostaglandin synthetase inhibitor (indomethacin, 1 μg/ml). All of the pharmacological antagonists were used in concentrations that inhibit ED_{50}-ED_{60} doses of their respective agonists (Altura & Altura, 1974; 1975; Altura, Edgarian & Altura, 1976; Edgarian & Altura, 1976).

Cumulative $CaCl_2$ contractile dose-response curves were obtained on aortic strips and portal veins in the absence and then the presence of various concentrations of ketamine. These tissues were first subjected to Ca^{2+}-free Krebs-Ringer bicarbonate solution (30 min exposure) and then to a subsequent Ca^{2+}-free high potassium-depolarizing solution (for 45 min), as described previously (Altura & Altura, 1974; 1975). In the Ca^{2+}-free potassium-depolarizing solution 118 mM NaCl was iso-osmotically replaced with KCl (total K^+, 123.9 mM). These results are expressed as a percentage of control (in absence of ketamine) maximal $CaCl_2$-induced contractile responses.

In some experiments, vascular tissues, displaying spontaneous, rhythmic activity, were exposed for 30 s to 10 min to Ca^{2+}-free Krebs-Ringer bicarbonate solution.

Statistical analyses

Where appropriate, the means (±s.e. mean) of the responses in control and experimental (with ketamine) vascular tissues were compared for statistical signifi-

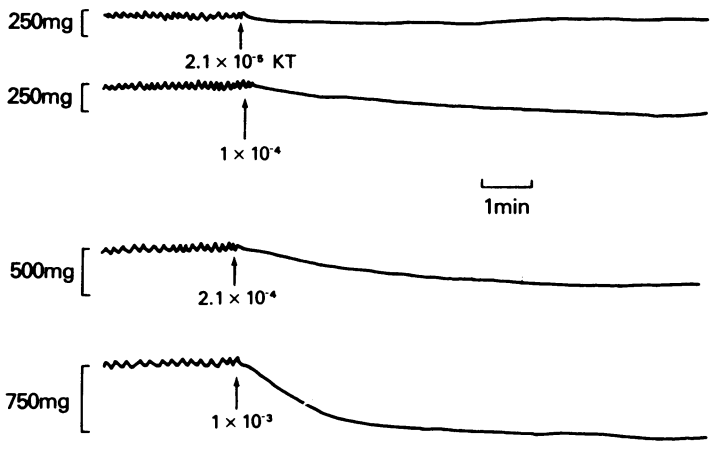

Figure 1 Influence of various concentrations of ketamine on development of spontaneous mechanical activity in a single isolated rat aortic strip. Arrows indicate points at which tissue was exposed to ketamine (KT, M concentration). Values on left in this figure and others represent tension.

cance by means of Student's *t* test, paired *t* test, or analysis of variance (Finney, 1964).

Drugs and chemicals

The following drugs and chemicals were used in the present studies: phentolamine (Regitine, Ciba-Geigy), propranolol hydrochloride (Aldrich Chemical Co.), methysergide maleate (Sandoz Ltd.), atropine sulphate (Mann Research Laboratories), diphenhydramine hydrochloride (Benadryl, Parke Davis and Co.), indomethacin (Merck Sharpe and Dohme), ketamine hydrochloride (Bristol Laboratories; Parke Davis and Co.), adrenaline (epinephrine) hydrochloride (Aldrenalin Chloride, Parke Davis and Co.), noradrenaline (norepinephrine) bitartrate (Calbiochem. Co.), angiotensin II amide (Hypertensin, Ciba-Geigy), 5-hydroxytryptamine (serotonin) creatinine sulphate (Sigma Chemical Co.), vasopressin (synthetic lysine vasopressin, Sandoz Ltd.), and KCl (Fisher Scientific Co.). All drugs, solutions, and chemicals were prepared immediately before use.

Table 1 Ketamine-induced lowering of base-line tension in isolated aortic strips of the rat

Ketamine (M)	n	*Loss in base-line resting tension* (mg) (mean ± s.e. mean)
1×10^{-5}	8	−12.5 ± 6.5
2.1×10^{-5}	15	−82.7 ± 6.3*
1×10^{-4}	16	−168.0 ± 18.5*
2.1×10^{-4}	20	−270.3 ± 21.4*
1×10^{-3}	20	−387.5 ± 36.6*

* Significantly different from control tension ($P < 0.01$).

Results

Influence of different concentrations of ketamine on spontaneous mechanical activity and basal tension

Figures 1 and 2 show recordings of typical changes in base-line tension and spontaneous mechanical activity in a single isolated aorta and a single portal vein, before and after the addition of various concentration of ketamine. A concentration of as little as 2.1×10^{-5} M ketamine inhibited the development of spontaneous mechanical activity, and lowered base-line tension, in rat aortic strips (Figure 1). (All rat aortic strips do not always exhibit spontaneous mechanical activity when incubated in normal Krebs-Ringer bicarbonate solution, see Altura & Altura (1974). In these cases, ketamine still induced a concentrated-related lowering of base-line tension.) The greater the concentration of ketamine, the more rapidly the inhibition became manifest, and the more the base-line tension was lowered in rat aorta (Figure 1; Table 1). Although the data in Figure 2 and Table 2 demonstrate that development of spontaneous mechanical activity was also inhibited in rat portal venous muscle by ketamine in a concentration-related manner, there were some diffferences from that seen in rat aorta. For example, the threshold inhibitory concentrations for ketamine in rat aortic strips was 2.1×10^{-5} M (Table 1), but it was 5 times higher in rat portal vein (Table 2); and ketamine lowered base-line tension in aortic (Figure 1) but not venous smooth muscle (Figure 2).

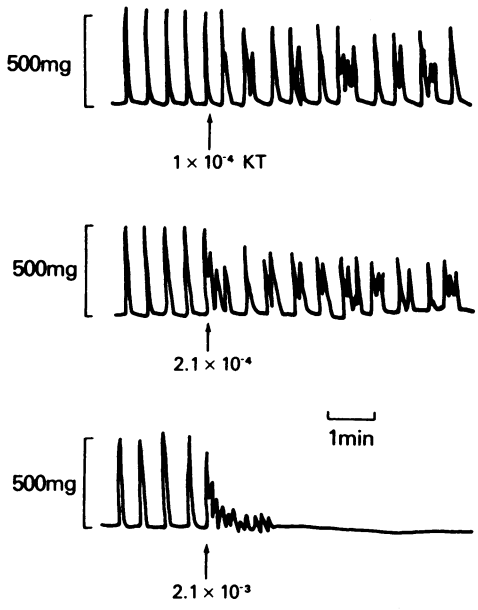

Figure 2 Influence of various concentrations of ketamine (KT, M) on development of spontaneous mechanical activity in a single isolated rat portal vein.

Influence of ketamine on contractions of rat aortic strips and portal veins induced by single doses of vasoactive agents

Figure 3 indicates that equi-potent contractions induced by four vasoactive agents, used on rat aortae, exhibited the following order of sensitivity to inhibition by ketamine; vasopressin > angiotensin > KCl > noradrenaline. Equi-potent contractions induced by three of these agonists on rat portal vein exhibited, qualitatively, a similar order of sensitivity to inhibition by ketamine: angiotensin > KCl > noradrenaline (Figure 4).

Influence of ketamine on catecholamine, peptide and potassium contractile concentration-effect curves of rat aortic strips and portal veins

Catecholamine (Figure 5), KCl (Figure 6), angiotensin (Figure 7) and vasopressin (Figure 8) concentration-effect curves on rat aortae and portal veins, in the presence of increasing doses of ketamine were shifted progressively to the right concomitant with progressive, marked reductions in maximum contractile responses. It should be noted that all of these inhibitory, as well as the relaxant (described below), effects of ketamine were rapidly reversible (i.e., within minutes) after washing with normal Krebs-Ringer bicarbonate solution.

Relaxation of established vasoactive agonist-induced contractions of aortic strips and portal veins

Only single dose experiments were performed. Submaximal concentrations of the agonists, noradrenaline, adrenaline, KCl, angiotensin and vasopressin, were used. Aortic strips (Figure 9) and portal veins (Figure 10) previously contracted by treatment with the catecholamines, peptides and KCl were dose-dependently relaxed upon the addition of ketamine (5×10^{-5} to 2.1×10^{-3} M). This relaxant action increased with time and with increasing concentration. In some cases, high concentrations of ketamine (i.e., 2.1×10^{-3} M or higher) relaxed the submaximal contractions below the base-line resting tension of the aortic strips (Figure 9).

Failure of pharmacological antagonists and of a prostaglandin synthetase inhibitor to either prevent or mimic the inhibitory actions of ketamine

Propranolol, phentolamine, methysergide, atropine, or diphenhydramine (see Methods for concentrations) could not prevent, attenuate or mimic any of the

Table 2 Effects of ketamine hydrochloride on spontaneous contractions of rat hepatic-portal veins

Ketamine (M)	n	*Contractile tension (mg)* (mean ± s.e. mean)	*Frequency (contractions/min)* (mean ± s.e. mean)
0	34	557.0 ± 18.3	3.77 ± 0.14
2.1×10^{-5}	15	509.7 ± 41.4	3.71 ± 0.19
1.0×10^{-4}	18	471.5 ± 25.2*	3.69 ± 0.18
2.1×10^{-4}	22	415.7 ± 30.7*	3.89 ± 0.16
2.1×10^{-3}	22	0*†	0*†

* Significantly different from paired controls ($P < 0.01$).
† Produced 7.78 ± 0.52 spontaneous contractions per min during initial 90 s (with a mean tension of 85.7 ± 9.8 mg.), then obliterated.

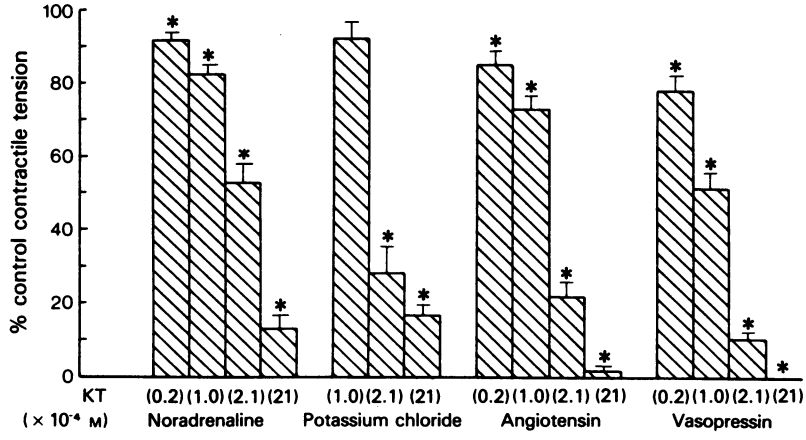

Figure 3 Differential sensitivity of equipotent noradrenaline (5 ng/ml), KCl (10 mM), angiotensin 11 (5 ng/ml), and vasopressin (2 mu/ml)-induced concentrations in rat aortic strips to inhibition by increasing doses of ketamine ($\times 10^{-4}$ M). n = 6–12 different preparations for each agonist. Vertical lines show s.e. mean. Mean values significantly different from controls ($P < 0.02$) are indicated by asterisks. Control isometric tensions were: noradrenaline (720 ± 40 mg); KCl (705 ± 35 mg); angiotensin (732 ± 42 mg); and vasopressin (685 ± 37 mg). Although not shown, equipotent adrenaline-induced contractions were inhibited, qualitatively, like those induced by noradrenaline.

above actions of ketamine on either rat aortic or portal venous smooth muscle (n = 4–6 animals each). Although indomethacin attenuated the portal vein spontaneous contractions by 30 to 50%, it did not alter the inhibitory effects of ketamine either in the veins or in the aortae (n = 4 animals).

Unusual potentiating action of ketamine on 5-hydroxytryptamine-induced contractions in rat aortae and portal veins

In contrast to the concentration-related inhibitory actions of ketamine on catecholamine, peptide and

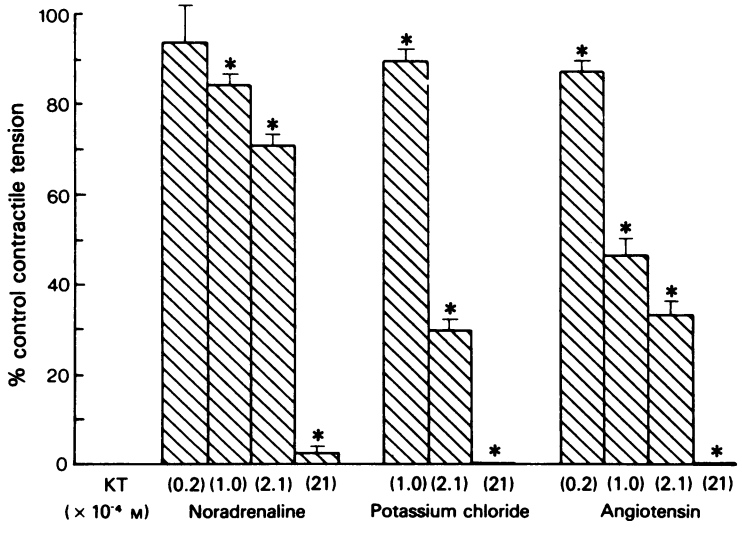

Figure 4 Differential sensitivity of equipotent noradrenaline (0.2 μg/ml), KCl (20 mM), and angiotensin II (0.5 ng/ml)-induced contractions in rat portal veins to inhibition by increasing concentrations of ketamine ($\times 10^{-4}$ M). n = 6–12 different preparations for each agonist. Control isometric tensions were: noradrenaline (965 ± 67 mg); KCl (1052 ± 86 mg); and angiotensin (942 ± 92 mg). *Mean values significantly different from controls ($P < 0.02$).

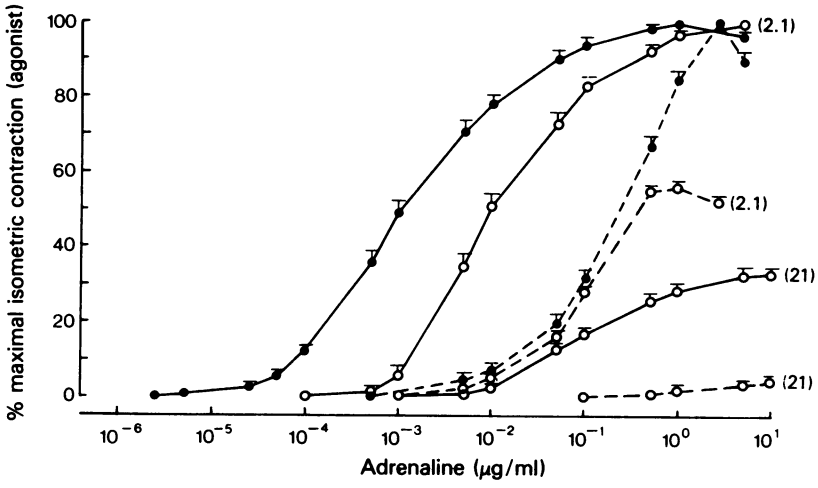

Figure 5 Effects of ketamine on adrenaline contractile concentration-effect curves in rat aortic strips and portal veins. Rat aorta (controls ●——●; ketamine [$\times 10^{-4}$ M] ○——○); portal vein (controls ●- - -●; ketamine [$\times 10^{-4}$ M] ○- - -○). Twelve different preparations were used for each vessel type. 100% isometric contractile tension on aorta = 1, 572 ± 86 mg. 100% isometric contractile tension on portal vein = 2, 102 ± 158 mg. Note that both the ED_{50}s and thresholds for adrenaline are progressively shifted to higher concentrations in the presence of ketamine. All experimental dose-response curves are significantly different from paired controls ($P < 0.05$).

potassium-induced contractions, noted above, ketamine (2×10^{-6} to 1×10^{-4} M) was found to potentiate markedly 5-HT-induced contractions of both aortic and venous smooth muscle (Figure 11). A concentration of 2×10^{-5} ketamine usually produced the greatest and most consistent potentiation. Although this potentiation was noted in 42 out of 52 animals, it was only observed if the ketamine was added after 5-HT had initiated a response in the two vessel types. Concentrations of ketamine higher than 1×10^{-4} M always resulted in a concentration-related attenuation of 5-HT-induced contractions, irrespec-

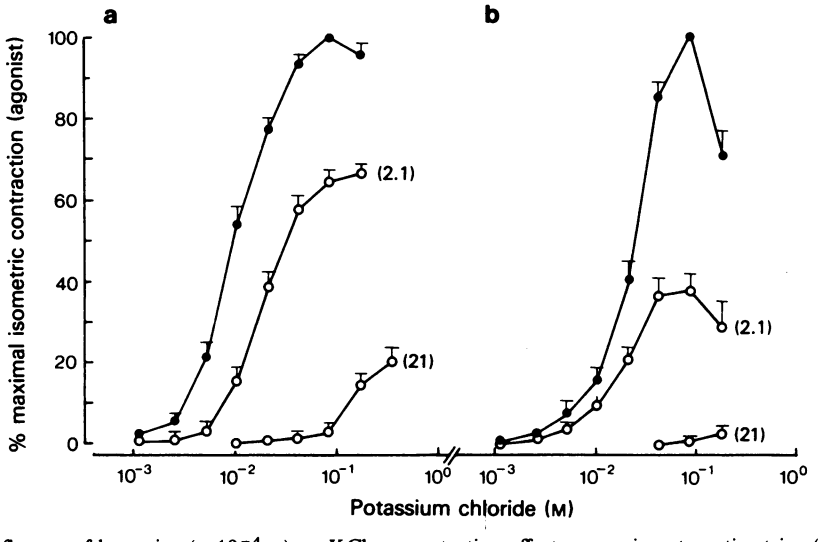

Figure 6 Influence of ketamine ($\times 10^{-4}$ M) on KCl concentration-effect curves in rat aortic strips (a) and portal veins (b). Controls = (●——●); ketamine = (○——○). Twelve different preparations were used for each vessel type. 100% isometric contractile tension on aorta = 1,220 ± 92 mg. 100% isometric contractile tension on portal vein = 1506 ± 122 mg. Note that both the ED_{50}s and thresholds for KCl are progressively shifted to higher concentrations in the presence of ketamine. All experimental dose-response curves are significantly different from paired controls ($P < 0.02$).

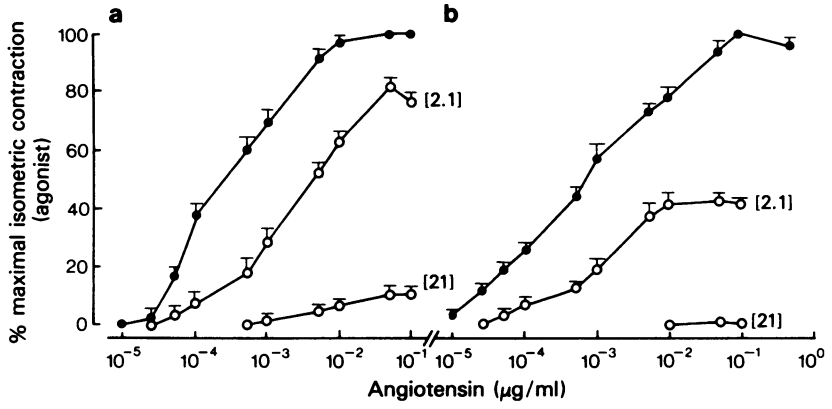

Figure 7 Influence of ketamine ($\times 10^{-4}$ M) on angiotensin concentration-effect curves in rat aortic strips (a) and portal veins (b). Controls = (●); ketamine = (○). Five different preparations were used for each vessel type. 100% isometric contractile tension on aorta = 1,376 ± 78 mg. 100% isometric contractile tension on portal vein = 1,095 ± 28 mg. Note that both the ED_{50}s and thresholds for angiotensin are progressively shifted to higher concentrations in the presence of ketamine. All experimental dose-response curves are significantly different from paired controls ($P < 0.01$).

tive of whether the ketamine was added before, or after, the 5-HT. It should be noted that contractions induced by other types of amine (catecholamine, phenylephrine), peptide (vasopressin, angiotensin II), ion (K^+, Ba^{2+}) or prostaglandin agonists were not potentiated by low doses of ketamine on either rat aortae or portal veins ($n = 42$ experiments).

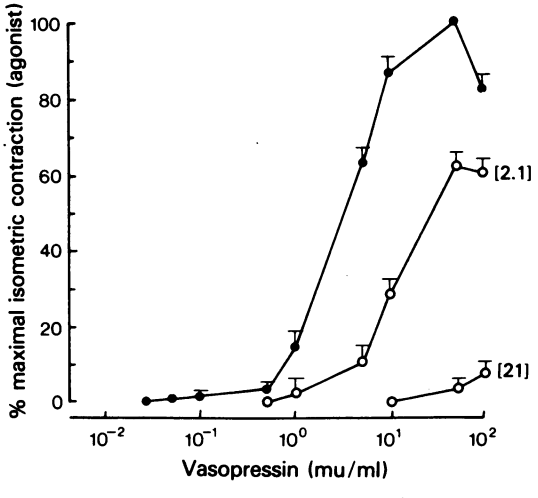

Figure 8 Influence of ketamine ($\times 10^{-4}$ M) on vasopressin concentration-effect curves in rat aortic strips. Twelve different preparations were used. Controls = (●); ketamine ($\times 10^{-4}$ M) = (○). 100% isometric contractile response = 1,062 ± 64 mg. Both experimental dose-response curves are significantly different from the paired controls ($P < 0.02$).

Influence of removal of calcium on spontaneous mechanical activity and base-line tension in rat aortic and portal venous smooth muscle

The above data seemed to indicate that the inhibitory effects of ketamine might be due to a non-specific, but direct, action either at and/or beyond the vascular muscle cell membranes. As the spontaneous contractile activity in vascular smooth muscle is known to be dependent upon influx of calcium ions (see recent review by Altura & Altura, 1978), we exposed the two types of blood vessels to Ca^{2+}-free Krebs-Ringer solution in order to determine whether the resultant effects, on base-line tension and spontaneous activity, would mimic the actions of high concentrations of ketamine. As can be seen in Figure 12, exposure of both vessels to a Ca^{2+}-free environment produces results identical to the effects of $1–2 \times 10^{-3}$ M ketamine shown in Figures 1 and 2, namely, an almost immediate loss in spontaneous mechanical activity in both tissues and a marked loss in base-line tension in the rat aorta.

Effects of ketamine on calcium chloride-induced contractions of aortic strips and portal veins

Ketamine not only reduced the magnitude of calcium-induced contractions of potassium-depolarized aortic strips and portal veins, but increasing ketamine concentrations caused progressive rightward shifts of the Ca^{2+} concentration-effect curves (Figure 13). For example, both the threshold concentrations and the ED_{50}s for calcium chloride-induced contractions were significantly increased by ketamine (Figure 13).

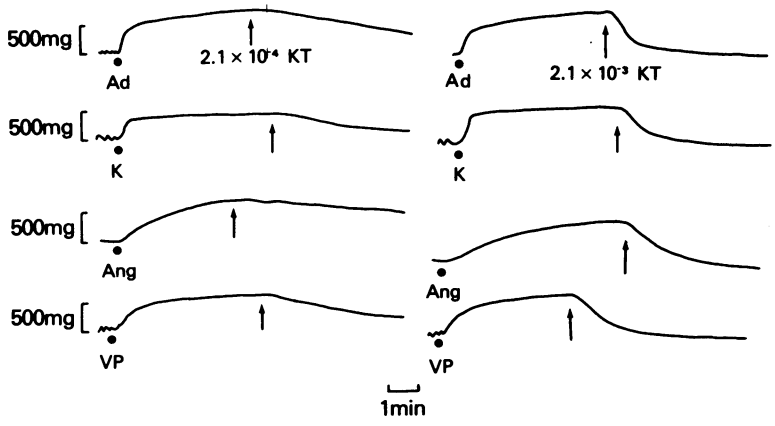

Figure 9 Relaxation of vasoactive agent-induced contractions of isolated rat aorta by ketamine (KT, left panel 2.1×10^{-4} M; right panel 2.1×10^{-3} M). The agonist concentrations added at dots were: adrenaline (Ad 5 ng/ml), KCl (K 10 mM), angiotensin (Ang 2.5 ng/ml) and [8-lysine]-vasopressin (VP 2 mu/ml).

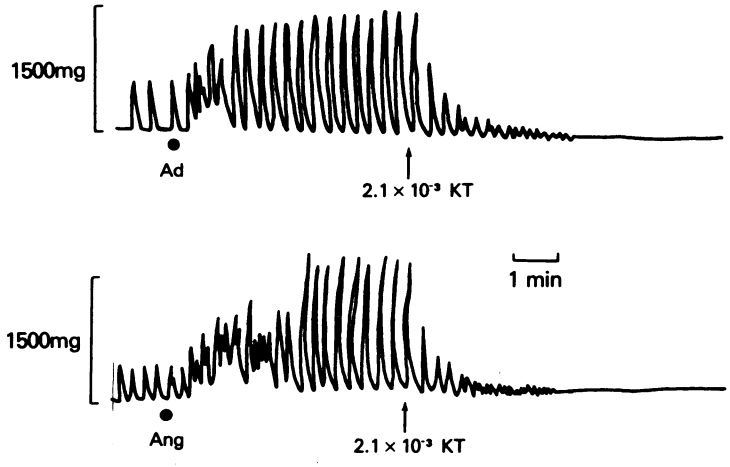

Figure 10 Relaxation of adrenaline (Ad)- and angiotensin (Ang)-induced contractions of isolated rat portal vein by ketamine (KT). The agonist concentrations were: adrenaline (0.5 μg/ml) and angiotensin (0.2 μg/ml).

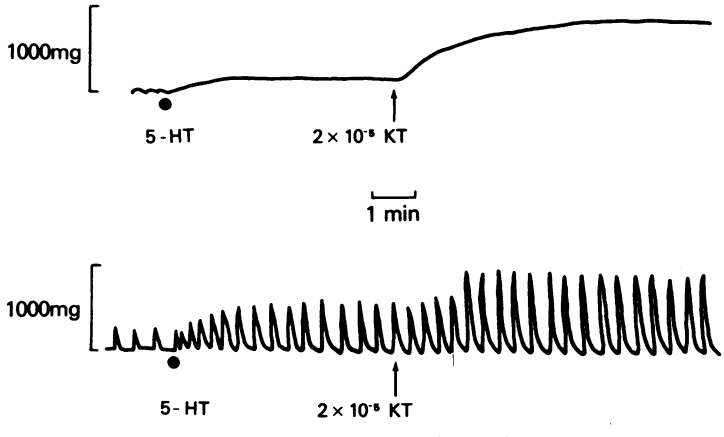

Figure 11 Ketamine potentiates 5-hydroxytryptamine (5-HT)-induced contractions of rat aorta (upper trace) and portal vein (lower trace). The 5-HT concentrations were: aorta (0.025 μg/ml); vein (0.25 μg/ml).

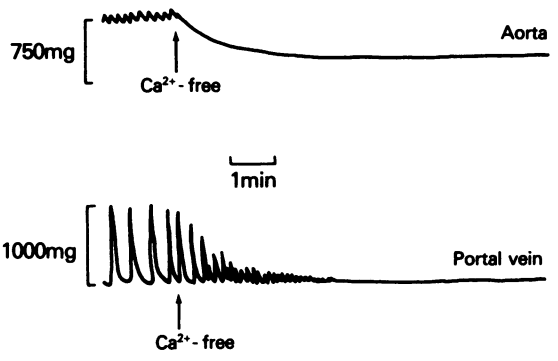

Figure 12 Influence of removal of calcium on spontaneous mechanical activity and base-line tension in rat aorta and portal vein.

Discussion

Our experiments indicate that ketamine hydrochloride inhibits, dose-dependently, the spontaneous mechanical contractions of rat aortae and portal veins, decreases the sensitivity of rat aortae and portal veins to different vasoactive agonists, and attenuates the contractile responses of aortic and venous smooth muscle to vasoactive stimuli. In addition, the results show that 5-HT-induced contractions are markedly, and specifically, potentiated by low doses of ketamine; that is no other contractile agonist tested showed a similar propensity for potentiation by any concentration of ketamine.

The plasma levels (e.g., 6×10^{-5} to 2×10^{-4} M; Cohen & Trevor, 1973; Cohen, Chan, Way & Trevor, 1973) of anaesthetic doses of ketamine (20 to 40 mg/kg), after its intravenous injection into rats, are highest within the first few minutes. During this time, there is usually a short-lived vasodepressor response (Chang *et al.*, 1969). Since the potent, fast-acting (as well as easily reversible) inhibitory effects observed here with ketamine take place with similar concentrations of the amine-anaesthetic, it seems reasonable to suggest that the initial fall in blood pressure, at least in the rat, is due, at least in part, to a direct action of ketamine on vascular smooth muscle. Although it has been suggested by several workers that either actions on the sympathetic nervous system (Chang *et al.*, 1969; Traber & Wilson, 1969) or a cocaine-like action of ketamine on vascular muscle (Montel, Starke, Gorlitz & Schumann, 1973; Nedergaard, 1973) may account for its pressor activity in several mammalian species, recent experiments by Clanachan & McGrath (1976) and Clanachan, McGrath & MacKenzie (1976), using pithed rats, α-adrenoceptor blocking agents, depletion of tissue noradrenaline and adrenalectomy would seem to eliminate mediation by either liberation of catecholamines or action on adrenergic vascular neuroeffectors, at least for the rat. Our results demonstrating a unique, and specific, potentiation by ketamine of 5-HT-induced contractile responses could, however, explain the secondary peripherally-mediated pressor response observed in the rat, after ketamine administration and possibly for other mammals as well. It is interesting that the concentration (2×10^{-5} M) which gave us the maximum potentiation, on both the rat arterial and venous smooth muscles, is the concentration observed in plasma of rats 3 to 10 min after intravenous injection of ketamine (Cohen & Trevor, 1973; Cohen *et al.*, 1973); this time-frame usually parallels the period of short-lived pressor action of ketamine in the rat.

The present observations indicate that high concen-

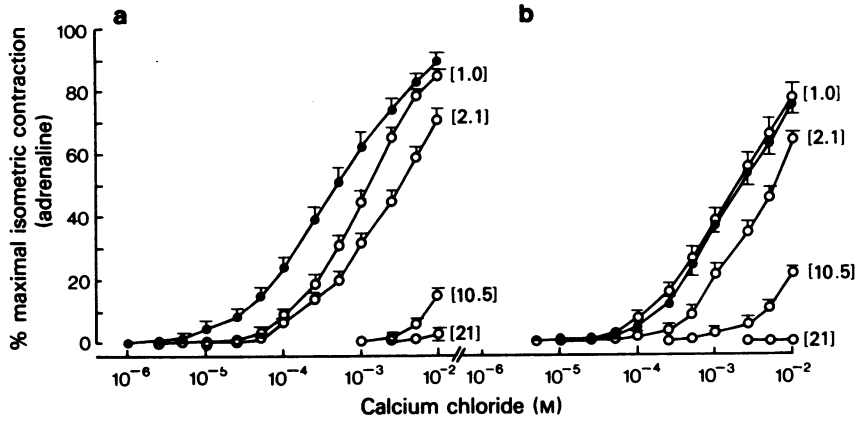

Figure 13 Influence of ketamine [$\times 10^{-4}$ M] on calcium chloride-induced contractions of potassium-depolarized rat aortae (a) and portal veins (b). $n = 5$. 100% isometric contractile tension for aortae = 1,572 ± 136 mg. 100% isometric contractile tension for portal veins = 2,242 ± 162 mg. Controls (●); ketamine (○).

trations of ketamine (e.g., 2.1×10^{-3} M) completely abolish spontaneous and neurohumoral agonist-induced contractions, as well as Ca^{2+}-induced contractions of both types of vascular smooth muscle used here. In addition, the basal tone of rat aortae is also abolished at this concentration of ketamine. These observations could be used to suggest that ketamine, may block transmembrane calcium-ion movements, as do calcium antagonists such as verapamil, lanthanum, SKF 525A and cinnarizine (Godfraind & Kaba, 1972; Bohr, 1973; Godfraind, 1976). This would explain the abolition of the spontaneous contractions, basal tone, as well as the agonist-induced contractions, since these are all dependent upon Ca^{2+} (see recent review by Altura & Altura, 1978). This could also explain the increase in threshold concentration and ED_{50} observed for all agonists as the concentration of ketamine in the bath fluid is increased. We have reported that at least two other types of intravenous anaesthetic agents, barbiturates and ethanol, exert similar depressant actions on the vessels used here (Altura & Altura, 1975; Altura *et al.*, 1976; Edgarian & Altura, 1976) and can in anaesthetic concentrations decrease ^{45}Ca uptake in these vessels (Turlapaty, Altura & Altura, 1979; Altura, Altura, Carella, Turlapaty & Weinberg, 1980). However, it is also possible that ketamine could accelerate the rate of Ca^{2+} sequestration or calcium efflux. Further experiments to test these tenets are in progress.

In both the aortae and portal veins, all concentration-effect curves were shifted to the right in a non-parallel manner in the presence of increasing concentrations of ketamine, and even the maximum tensions induced by adrenaline and noradrenaline were reduced. It is reasonable to suggest that ketamine also exerts an intracellular effect in addition to its extracellular (or membrane) action discussed above, since the latter agonists are known, at high concentrations, to utilize intracellular Ca^{2+} for their contractile responses (Bohr, 1973). Ketamine is thought to penetrate rapidly into cells (Cohen *et al.*, 1973; Dundee & Wyant, 1974). An interaction of ketamine, with intracellularly-bound calcium could prevent this divalent cation from being released from its intracellular storage sites, thus inhibiting one of the components responsible for vascular muscle contractions elicited by catecholamines (Van Breemen, Farinas, Gerba & McNaughton, 1972). This would result in inhibition of maximum contractions for adrenaline and noradrenaline, exactly as observed on the aortae and veins in the present study.

It is unlikely that the inhibitory effects of ketamine on contractions induced by different vasoactive agents could be solely a reflection of inhibition of cellular metabolism. If ketamine were acting via such a mechanism, then the equipotent, submaximal contractions induced by the four agonists on both types of vessels (Figures 3 and 4) should have been inhibited to the same extent by each concentration of ketamine, rather than exhibit a relative order of sensitivity to the anaesthetic agent, where vasopressin > angiotensin > KCl > adrenaline.

The mechanism for the specific potentiation of 5-HT-contractions by certain concentrations of ketamine is not elucidated in this paper. However, our preliminary findings (authors' unpublished data) indicate that: (a) 5-HT antagonists (e.g., methysergide, bromo-lysergic acid diethylamide or a reduction in $[Ca^{2+}]_o$ can abolish this unique synergistic interaction; (b) the 5-HT neuronal uptake inhibitor, fluoxetine (Fuller, Snoddy & Molloy, 1975) can partially substitute for ketamine in potentiating 5-HT-induced contractions in the vessels used here; and (c) phencyclidine, the molecule from which ketamine is derived, can also enhance 5-HT-induced contractions. Such preliminary findings suggest to us that ketamine, in the presence of $[Ca^{2+}]_o$, may be able to enhance 5-HT binding to its vascular receptors, and act to prevent 5-HT inactivation by preventing neuronal reuptake, thus possibly accounting for the unusual potentiation noted herein. Further experiments to test this possibility are now in progress. It is noteworthy that ketamine hydrochloride has recently been shown to prevent radio-labelled 5-HT accumulation by rat brain synaptosomal-rich fractions (Azzaro & Smith, 1977).

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References

ADAMS, H.R., PARKER, J.L. & MATHEW, B.P. (1977). The influence of ketamine on inotropic and chronic responsiveness of heart muscle. *J. Pharmac. exp. Ther.*, **201**, 171–183.

ALTURA, B.M. (1972). Sex as a factor influencing the responsiveness of arterioles to catecholamines. *Eur. J. Pharmac.*, **20**, 261–265.

ALTURA, B.M. & ALTURA, B.T. (1970). Differential actions of substrate depletion on drug-induced contractions of rabbit aorta. *Am. J. Physiol.*, **219**, 1698–1705.

ALTURA, B.M. & ALTURA, B.T. (1974). Magnesium and contraction of arterial smooth muscle. *Microvasc. Res.*, **7**, 145–155.

ALTURA, B.T., & ALTURA, B.M. (1975). Barbiturates and

aortic and venous smooth-muscle function. *Anesthesiology*, **43**, 432–444.

ALTURA, B.M. & ALTURA, B.T. (1977). Influence of sex hormones, oral contraceptives and pregnancy on vascular muscle and its reactivity. In *Factors Influencing Vascular reactivity*, ed. Carrier, O., Jr. & Shibata, S. pp. 221–254, Tokyo: Igaku-Shoin Ltd.

ALTURA, B.T., & ALTURA, B.M. (1978). Factors affecting vascular responsiveness. In *Microcirculation*, Vol. 2, ed. Kaley, G. & Altura, B.M. pp. 547–615, Baltimore: Univ. Park Press.

ALTURA, B.M., ALTURA, B.T., CARELLA, A., TURLAPATY, P.D.M.V. & WEINBERG, J. (1980). Vascular smooth muscle and general anesthetics. In *Cardiovascular Actions of General Anesthetics* ed. Altura, B.M. Fedn Proc.

ALTURA, B.M., EDGARIAN, H. & ALTURA, B.T. (1976). Differential effects of ethanol and mannitol on concentration of arterial smooth muscle. *J. Pharmac. exp. Ther.*, **197**, 352–361.

AZZARO, A.J. & SMITH, D.J. (1977). The inhibitory actions of ketamine HCl on [^{3}H]-5-hydroxytryptamine accumulation by rat brain synaptosomal-rich fractions: comparison with [^{3}H]-catecholamine and [^{3}H]-γ-aminobutyric acid uptake. *Neuropharmac.*, **16**, 349–356.

BOHR, D.F. (1973). Vascular smooth muscle updated. *Circulation Res.*, **32**, 665–672.

CHANG, P., CHAN, K.E. & GANENDRAN, A. (1969). Cardiovascular effects of 2-(O-chlorophenyl)-2-methyl-aminocyclohexanone (Cl-581). *Br. J. Anaesth.*, **41**, 391–395.

CLANACHAN, A.S. & MCGRATH, J.C. (1976). Effects of ketamine on peripheral autonomic nervous system of the rat. *Br. J. Pharmac.*, **58**, 247–252.

CLANACHAN, A.S., MCGRATH, J.C. & MACKENZIE, J.E. (1976). Cardiovascular effects of ketamine in the pithed rat, rabbit and cat. *Br. J. Anaesth.*, **48**, 935–939.

COHEN, M.L., CHAN, S.-L., WAY, W.L. & TREVOR, A.J. (1973). Distribution in the brain and metabolism of ketamine in the rat after intravenous administration. *Anesthesiol.*, **39**, 370–376.

COHEN, M.L. & TREVOR, A.J. (1973). On the cerebral accumulation of ketamine and the relationship between metabolities of the drug and its pharmacological effects. *J. Pharmac. exp. Ther.*, **189**, 351–358.

CORSEN, G. & DOMINO, E.F. (1966). Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative Cl-581. *Anesth. Analg.* **45**, 29–39.

DOMINO, E.F., CHODOFF, P. & CORSSEN, G. (1965). Pharmacologic effects of Cl-581, a new dissociative anesthetic in man. *Clin. Pharmac. Ther.*, **6**, 279–290.

DOWDY, E.G. & KAYA, K. (1968). Studies of the mechanism of cardiovascular responses to Cl-581. *Anesthesiol.*, **29**, 931–943.

DUNDEE, J.W. & WYANT, G.M. (1974). *Intravenous Anaesthesia.* Edinburgh: Churchill Livingstone.

EDGARIAN, H. & ALTURA, B.M. (1976). Ethanol and contraction of venous smooth muscle. *Anesthesiol.*, **44**, 311–317.

FINNEY, D.J. (1964). *Statistical Method in Biological Assay.* pp. 99–138, London: Charles Griffin and Co.

FULLER, R. W., SNODDY, H.D. & MOLLOY, B.B. (1975). Blockade of amine depletion by nisoxetine in comparison to other uptake inhibitors. *Psychopharmac. Comm.*, **1**, 455–464.

GODFRAIND, T. (1976). Calcium exchange in vascular smooth muscle, action of noradrenaline and lanthanum. *J. Physiol.*, **260**, 21–35.

GODFRAIND, T. & KABA, A. (1972). The role of calcium in the action of drugs on vascular smooth muscle. *Archs int. Pharmacodyn. Ther.*, **196** (Suppl.), 35–49.

HAMILTON, W.K. (1976). Ketamine today. In *Anaesthesia and Pharmacology.* ed. Spierdijk, J., Feldman, S.A. & Mattie, H. pp. 136–138. Baltimore: Williams & Wilkins Co.

HOROWITZ, L.D. (1977). Effects of intravenous anesthetic agents on left ventricular function in dogs. *Am. J. Physiol.*, **232**, H44–H48.

HUG, C.C., JR. (1979). Pharmacology-anesthetic drugs. In *Cardiac Anesthesia.* ed. Kaplan, J.A. pp 3–37. New York: Grune & Stratton.

JOHNSTONE, M. (1976). The cardiovascular effects of ketamine in man. *Anaesthesia*, **31**, 873–882.

LIVINGSTON, A. & WATERMAN, A.E. (1977). Influence of age and sex on the duration of action of ketamine in the rat. *Br. J. Pharmac.*, **59**, 491 P.

MCCARTHY, D.A., CHEN, G., KAUMP, D.H. & ENSOR, C. (1965). General anesthetic and other pharmacological properties of 2-(O-chlorophenyl)-2-methylamino cyclohexanone HCl (Cl-581). *J. New Drugs*, **5**, 21–33.

MCGRATH, J.C. & MACKENZIE, J.E. (1977). The effects of intravenous anaesthetics on the cardiovascular system of the rabbit. *Br. J. Pharmac.*, **61**, 199–212.

MONTEL, H., STARKE, K., GORLITZ, B.D. & SCHUMMANN, H.J. (1973). Tierexperimentelle Untersuchungen zur Wirkung des Ketamins auf periphere sympathische Nerven. *Anaesthetist* **22**, 111–116.

NEDERGAARD, O.A. (1973). Cocaine-like effect of ketamine on vascular adrenergic neurones. *Eur. J. Pharmac.*, **23**, 153–161.

OCHSNER, A.J. (1977). Cardiovascular and respiratory responses to ketamine hydrochloride in the rhesus monkey (macaca mulatta). *Lab. Animal Sci.*, **27**, 69–71.

TRABER, D.L. & WILSON, R.D. (1969). Involvement of the sympathetic nervous system in the pressor response to ketamine. *Anesth. Analg.*, **48**, 248–252.

TRABER, D.L., WILSON, R.D. & PRIANO, L.L. (1968). Differentiation of the cardiovascular effects of Cl-581. *Anesth. Analg.*, **47**, 769–778.

TRABER, D.L., WILSON, R.D. & PRIANO, L.L. (1971). The effect of alpha-adrenergic blockade on the cardiopulmonary response to ketamine. *Anesth. Analg.*, **50**, 737–741.

TURLAPATY, P.D.M.V., ALTURA, B.T. & ALTURA, B.M. (1979). Ethanol reduces ^{45}Ca concentration in arterial and venous smooth muscle. *Experientia*, **35**, 639–640.

VAN BREEMEN, C., FARINAS, B.R., GERBA, P. & MCNAUGHTON, E.D. (1972). Excitation-contraction coupling in rabbit aorta studied by the lanthanum method for measuring cellular calcium influx. *Circulation Res.*, **30**, 44–54.

VIRTUE, R.W., ALANIS, J.M., MARI, M., LAFARGUE, R.J., VOGEL, J.H., METCALF, D.R. (1967). An anesthetic agent: 2-orthochlorophenyl, 2-methylamino cyclohexanone HCl (Cl-581). *Anesthesiol.*, **28**, 823–833.

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