THE RELAXANT EFFECT OF KETAMINE IN ISOLATED RABBIT AORTIC STRIPS

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SUMMARY

This study was undertaken to determine whether ketamine can exert any action on basal endothelium derived relaxing factor (s) release and vasodilator effect of acetylcholine on phenylephrine induced contractile responses in isolated rabbit aortic strips. Ketamine did not induce any contractile response in the aortic strips at various concentrations (10^{-8} to 10^{-3} M). Ketamine did not significantly alter phenylephrine-induced contractions at lower concentrations (10^{-8} to 10^{-5} M), but at higher concentrations (10^{-4} to 10^{-3} M) the depression caused by ketamine was significant in both endothelium intact and denuded strips. Propranolol, methysergide, atropine, diphenhydramine and indomethacine did not block the relaxant effect of ketamine. Pretreatment of the endothelium intact strips with ketamine (10^{-5} M) had no effect on the relaxant effect of acetylcholine which was observed on endothelium intact aortic strips. The relaxant effect of ketamine on the isolated rabbit aortic strips does not seem to interact with the changes in the release of EDRF from endothelial cells.

Key Words: Ketamine, EDRF, Rabbit Aorta.

INTRODUCTION

Ketamine, is a short-acting iv anesthetic, which has been shown to produce a marked increase in arterial blood pressure, heart rate and cardiac output (1). Cardiovascular stimulation associated with ketamine administration is thought to be due to sympathomimetic effects mediated within CNS structures (2), inhibition of interneuronal uptake of catecholamines (cocaine-like effect on postganglionic adrenergic neurons) and inhibition of extraneuronal noradrenaline uptake (3). Critically ill patients may respond to ketamine with an unexpected decrease in blood pressure (4), which is thought to result from the lack of sympathomimetic actions of ketamine to counterbalance its direct vasodilatory and myocardial depressant effects (4,5).

The interaction of ketamine with endothelium-derived relaxing factor (EDRF), a substance (s) released from vascular endothelium by various agonists (6) has not been studied on isolated vascular strips.

It is thus interesting to determine if ketamine is actually a vasodilatory agent. The present study was undertaken to investigate whether ketamine has an effect on EDRF release from vascular endothelial cells of rabbit isolated aortic strips or a direct action in these vascular beds.

MATERIALS AND METHODS

Segments of thoracic aorta were obtained from rabbits of either sex (1.8-2.5 kg) anesthetized with sodium pentobarbital (30 mg/kg, IV). The segments were placed in Krebs solution of the following composition (mmol/L): NaCl, 112; KCL, 5; NaHCO3, 25; NaH2 PO4, 1; CaCl2, 2.5; MgCl2, 0.5 and dextrose, 11.5;at room temperature, were carefully cleaned of fat and surrounding tissues and helically cut (4 mm wide, 2 cm long). Only two strips of each segments were used from each animal. The endothelium of one of the strips was removed by a rubber or wooden stick. Removal of endothelium was confirmed by the loss of relaxant response to acetylcholine (10^{-6} mol/L). Paired strips were suspended in a jacketed organ bath of 10 ml volume containing Krebs solution at 37°C and gassed with 95% 02 and 5% CO2 mixture and isometric contractions were recorded on a recorder (Ugo Basile Gemini 7070) by means of force-displacement transducer (Ugo Basile, 7003) under 1.0g initial tension. The strips were allowed to equilibrate for 2 h and were continously washed with Krebs solution at a flow rate of 2 ml/min. After the equilibration period, vascular strips were exposed to different concentrations of ketamine (10^{-8} to 10^{-3} mol/L) to determine whether ketamine caused contraction of vascular strips.

Cumulative-concentration-effect curves to Ach and ketamine were obtained by increasing the bath concentration.

In a second series of experiments, submaximal vaso-constriction was produced by adding phenylephrine to the organ bath at the concentration of 10^{-7} mol/L

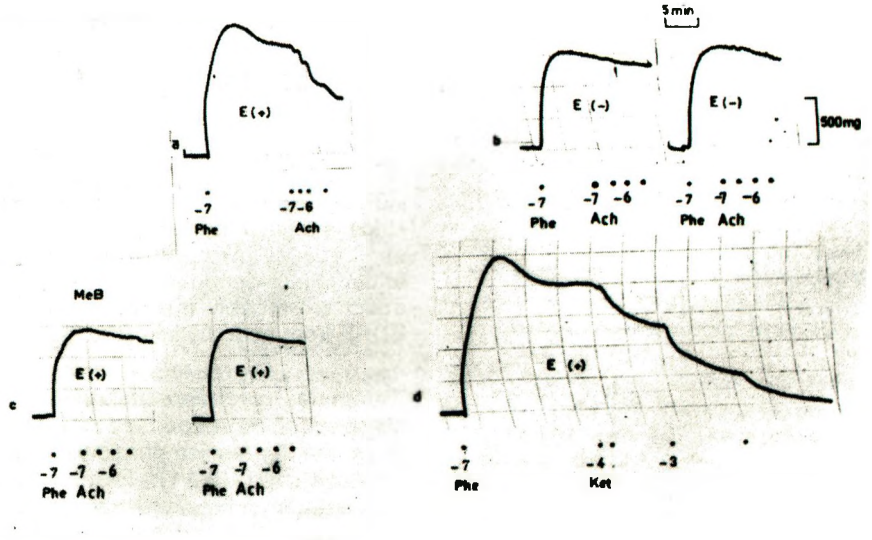

Figure 1: Recorder tracings indicating changes in relaxatile effects of acetylcholine (Ach) (Log mol/L)
a) endothelium intact E (+)
b) endothelium denuded E (-)
c) methylene blue (MeB) pretreated rabbit aortic strips.
Acetylcholine produced concentration-dependent relaxation only in E (+), but not E (-) and MeB-pretreated aortic strips.
d) The dose-dependent relaxant effect of ketamine (Ket) (Log mol/L) on Phenylephrine (Phe) (Log mol/L)-induced contractile response in rabbit aortic strip.

at endothelium intact strips,demonstrated with the presence of Ach-induced relaxation. After the determination of the concentration-response curve for acetylcholine (Ach), the strips were washed with normal Krebs solutions. Ketamine was then added to the incubation medium at the concentration of 10^{-5} M, which has no effect on the Phe-induced contractile responses, and was kept in contact with the strips for 45 min. Concentration-response curves for Ach were then redetermined.

In another series of experiments, the effect of ketamine at various concentrations (10^{-8} to 10^{-3} mol/L) on Phe (10^{-7} mol/L)- induced contractile responses was determined in both endothelium-intact and -denuded aortic strips. In addition, the effect of ketamine was investigated when methylene blue (MeB), an inhibitor of soluble guanylate cyclase (7), was added to the bathing medium at the concentration of 10^{-5} mol/L for 20 min. The vascular preparations were exposed to various pharmacological antagonists 30 min before adding ketamine to determine whether ketamine-induced responses were affected by beta-adrenoceptor blockade (propranolol hydrochloride, 0.5 mg/ml), cholinoceptor blockade (atropine sulphate, 0.5 mg/ml), histamine receptor blockade (diphenhydramine hydrochloride, 0.5 mg/ml) or a prostaglandin synhetase inhibitor (indometacine 1.0 mg/ml).

Data are shown as mean ± SEM and statistical differences were evaluated using Student's t test.

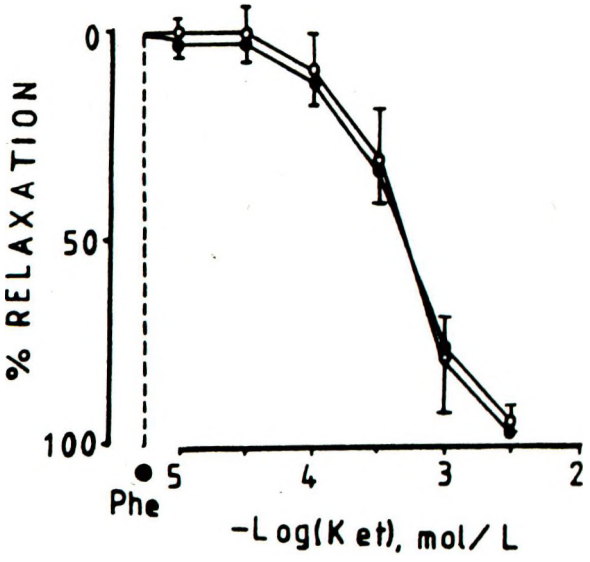

Figure 2: The relaxant effects of ketamine on Phe (10^{-7} mo l/L) induced contractions in endothelium intact (0-0) and denuded (●-●) rabbit aortic strips. Each point represents the mean value of 8 experiments and vertical bars show SEM.

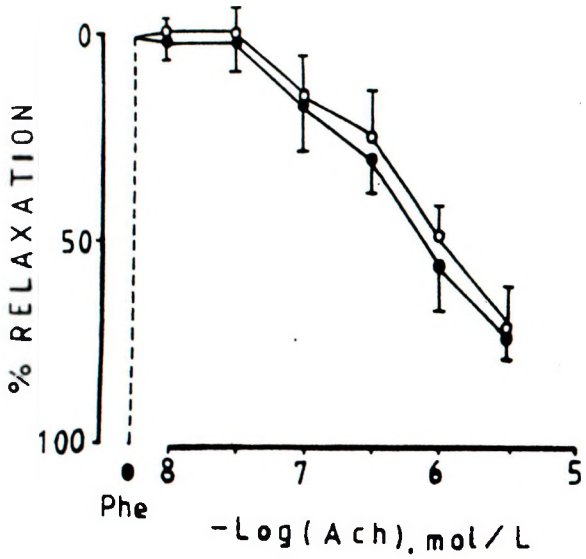

Figure 3: Concentration-response curves of acetylcholine on Phe (10^{-7} mol/L)- induced contractions in endothelium intact rabbit aortic strips (0-0) in presence and (●-●) absence of ketamine (10^{-5} mol/L). Each point represents the mean value of 8 experiments and vertical bars show SEM.

RESULTS

Ketamine did not induce any contractile responses on the aortic strips at 10^{-8} to 10^{-3} mol/L concentrations.

The effect of ketamine on the contraction elicited by submaximal concentration of the Phe (10^{-7} mol/L) was examined. Ketamine did not significantly alter Phe-induced contractions at 10^{-8} - 10^{-5}M concentrations, but it caused relaxation of both endothelium-intact and - denuded strips precontracted with phenylephrine (fig. 1d and 2). Propranolol, methysergide, atropine, diphenhydramine and indomethacine did not alter the relaxant effect of ketamine.

The concentration-response curves for Ach is shown in figure 1 a and 3. Addition of methylene blue to the bathing medium at the concentrations of 10^{-5} mol/L for 20 min both in endothelium intact strips and endothelium denuded strips abolished the Ach-induced concentration-dependent relaxation (fig. 1 b,c). After pretreatment of endothelium intact strips with ketamine (10^{-5} mol/L) no change was observed in the relaxant effect of Ach (fig.3)

DISCUSSION

The results of the present investigation clearly indicate that the vasodilator activity of Ach on Phe-induced contractions in the rabbit isolated aortic strips is related to the presence of vascular endothelium because Ach has no relaxant effect in both endothelium-denuded and MeB treated strips. This effect is probably mediated through the release of EDRF from endothelial cells (6).

Ketamine has been shown to produce biphasic blood-pressure responses in man, rats, rabbits and dogs; the depression phase usually appears first and is short-lived (8-11). Furthermore, it has been suggested that ketamine can also produce peripheral vasoconstriction in certain vascular beds (12, 13). In contrast to these reports, the present investigation indicated that ketamine had no vasoconstrictor effect and did not alter the release of EDRF from endothelial cells on isolated rabbit aortic strips. Therefore, the blood pressure increase induced by ketamine does not seem to due to either direct vascular smooth muscle responses or the changes in the release of EDRF from endothelial cells. Therefore, cocaine-like action on vascular smooth muscle (14), sympathomimetic actions induced by direct stimulation of CNS structures, direct effects on myocardium (15,16) may account for its pressor activity.

Several workers have demonstrated that anesthetic doses of ketamine can result in profound hypotension in certain species including monkeys, rabbits and rats (17). The short-lived vasodepressor response can be attributed to the highest concentration of ketamine after within the first few minutes it was administered intravenously at anesthetic doses (18).

Altura (19) showed that ketamine ($3x10^{-4}$ mol/L and the higher concentrations) dose-dependently attenuated contractions induced by several vasopressor agents either on rat aorta or portal veins. Similarly, we observed that ketamine (10^{-4} to 10^{-3} mol/L) depressed Phe-induced contractions on isolated rabbit aortic strips. This relaxant effect of ketamine was not affected by beta-adrenoceptor blockade, cholinoceptor blockade, histamine receptor blockade and prostaglandin synthesis inhibition.

It was shown that ketamine at higher doses abolished spontaneous and neurohumoral agonist-induced contractions as well as Ca^{++} -induced contractions on isolated rat aortae and portal veins (19). A possible explanation for this finding is the blockade of calcium-ion movements by ketamine just like calcium antagonists such as verapamil and lanthanum (20).

REFERENCES

1. Traber DL, Wilson RD, Priano LL. Differenciation of the cardiovascular effects of C1581. Anesth Analg 1968; 47:769.
2. Ivankovitch AD, Miletich DJ, Reimann C, Albrecht RF, Zahed B. Cardiovascular effects of centrally administered ketamine in goats. Anesth Analg 1974; 53: 924.
3. Salt PJ, Barnes PK, Beswick FJ. Inhibition of neuronal and extraneuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. Br J Anaesth 1979;51: 835.
4. Waxman K, Shoemaker WC, Lipmann M. Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg 1980;59:355.
5. While PF, Way WL, Trevar AJ.Ketamine-its pharmacology and therapeutic uses. Anesthesiology 1982;56:119.
6. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. Cir Res 1983;53:557.
7. Martin W.Villani GM,Jothinandan D.Selective blockade of endothelium-dependent glyceryl trinitrate induced relaxation by hemoglobine and methylene blue in rabbit aorta. J Pharmacol Exp Ther 1985;232:708.
8. Domino LG, Chodoff P,Corssen G.Pharmacologic effects of CI-581, a new dissociative anesthetic in man. Clin Pharmac Ther 1965;6:279.
9. McCarthy DA,Chen G, Kaump DH, Ensor C.General anesthetic and other pharmacological properties of 2-(0-chloro-phenyl)-2- methylamino cylohxanone HCl (CI-581).J New Drugs 1965;5021.
10. Dowdy EG, Kaya K.Studies of the mechanism of cardiovascular responses to CI-581. Anesthesiol 1968;29:931.
11. Virtue RW, Alanis JM, Mari M,Lafangue RJ, Vogel JH.Metcalf DR.An anesthetic agent: 2-orthochlorophenyl, 2-methyl-amino cyclohexanone HCl (CI-581). Anesthesiol 1967;28:823.
12. Traber DL,Wilson RD,Priano LL.The effect of alphaadrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 1971;50:737.
13. Johnstone M.The cardiovascular effects of ketamine in man. Anaesthesia 1976;31:873.
14. Nedergaard OA.Cocaine-like effect of ketamine on vascular adrenergic neurones. Eur J Pharmac 1973;23:153.
15. Traber DL, Wilson RD.Involvement of the sympathetic nervous system in the pressor response to ketamine. Anesth Analg 1969;48:248.
16. Barrigon S, De Miguel B, Tamargo J, Tejerina T. The mechanics of the positive inotropic action of ketamine on isolated atria of the rat. Br J Pharmac 1982;76:085.
17. Clanachan AS, McGrath JC,MacKenzie JE. Cardiovascular effects of ketamine in the pithed rat, rabbit and cat. Br J Anaesth 1976;48:935.
18. Chang P,Chan KE, Ganendran A.Cardiovascular effects of 2-(o-chlorophenyl)-2-methlamino cyclohexanone (CI-581). Br J Anaesth 1969;41:391.
19. Altura BM, Altura BT Anthong C.Effects of ketamine on vascular smooth muscle function. Br J Pharmac 1980;70:257.
20. Godfraind T.Calcium exchange in vascular smooth muscle, action of noradrenaline and lanthanum.J Physiol 1976;260:21.