EFFECTS OF KETAMINE ON ISOLATED HUMAN BRONCHIAL PREPARATIONS


Ketamine was reported to increase lung compliance and decrease airway resistance in patients suffering from asthma [1]. Many studies have been conducted on the bronchodilator properties of this compound, but the exact mechanism of action remains unclear. Conflicting data have been published on β-receptor activation by ketamine. In dogs exposed to an antigenic challenge, the effect of ketamine seems to depend on β-receptor stimulation, as pretreatment with propranolol blocks its action [2]. In contrast, with guineapig tracheal strip in vitro, bronchomotor effects do not depend on β activation [3]. In humans, β-dependent actions in addition to non-specific, non-competitive antagonism of the mediators have been postulated [4]. These data suggest that ketamine may exert species-dependent actions which may differ in vitro as opposed to in vivo. We have therefore investigated the interactions between ketamine and contractile agents in human bronchial preparations.

MATERIALS AND METHODS

With authorization of the French National Ethics Committee, human lung tissue was obtained from patients who had undergone surgery for bronchopulmonary carcinoma.

Following resection of a lung or a lobe, parts of the “normal” bronchi were identified by the surgeon and dissected free from the macroscopically abnormal lung tissues. The preparations were placed in cold Tyrode’s solution (composition (mmol litre⁻¹): NaCl 139.2, KCl 2.7, CaCl₂ 1.8, MgCl₂ 0.49, NaH₂PO₄ 0.4, glucose 5.5, pH 7.40) and stored at 4 °C for 12-18 h. Spirally cut bronchial preparations were placed in a 10-ml organ bath under initial loads of 3-5 g; these loads ensured optimal length of the preparations and that responses to contractile agents were maximal and reproducible. Tissues were allowed to equilibrate for 90 min in Tyrode’s solution at 37 °C, gassed with 5 % carbon dioxide in oxygen. At the end of the equilibration period, the lengths of the spirals were measured. At the end of the experiment, the wet weights of the preparations were recorded so as to measure tissue responsiveness in relation to weight. An isometric strain gauge (Narco F 60 Houston TX) and Narco Physiograph MK IV were used to record the changes in force. Cumulative concentration-effect curves to ketamine were generated after maximal contraction was induced with histamine, acetylcholine, barium chloride or potassium chloride. Each preparation was challenged...
twice with the concentration of agonist which produced maximal contraction, ensuring a reproducible maximal response; a third contraction was induced and increasing concentrations of ketamine were added to the tissue bath at 5-min intervals until the contraction was antagonized maximally.

Relaxations were expressed as a percentage of the maximal response developed with the contractile agonist (potency of ketamine).

Concentration–effect curves to histamine and acetylcholine were obtained also in the presence of various concentrations of ketamine (antagonism between ketamine and contractile agent).

In order to define the mechanism of action of ketamine, and especially the putative roles of β-receptor activation and of prostaglandins, we examined also the effect of ketamine on preparations pretreated with propranolol or indomethacin.

The concentration–effect curves were fitted by eye. The EC_{50} value (concentration of ketamine which decreased maximal contraction by 50%) was obtained as a measure of potency.

RESULTS

The bronchial preparations (n = 20) were physically homogeneous (length 42.3 (1.9) mm, wet weight 686.5 (84.5) mg (mean (SEM)).

Maximal responses were obtained with 50 μl of histamine 10^{-2} mol litre^{-1}, 100 μl of acetylcholine 10^{-2} mol litre^{-1}, 50 μl of barium chloride 1 mol litre^{-1}, and 1 ml of potassium chloride 1 mol litre^{-1}.

Responsiveness of tissues to contractile agents was expressed as tension (mg) per mg wet weight of tissue. Maximal tensions developed by bronchial preparations in response to agonists were: histamine, 112.7 (20.6) mg/mg wet tissue; acetylcholine, 106.3 (21.0) mg/mg wet tissue; barium chloride, 34.4 (6.5) mg/mg wet tissue; potassium chloride, 36.8 (7.2) mg/mg wet tissue.

Ketamine in concentrations approaching 10^{-2} mol litre^{-1} had no effect on the basal tone of the preparations. We examined the relaxant effect of ketamine (EC_{50} value) (table I) on maximally contracted bronchial preparations. Comparison of EC_{50} values indicates that the relaxation obtained with ketamine was constant irrespective of the agonist used and, in all instances, reached 100% (figs 1, 2). We also examined the antagonism of histamine and acetylcholine exerted by ketamine administered to bronchial preparations (figs 3, 4); the rightward shift in the concentration–effect curve to histamine and acetylcholine in the presence of ketamine 10^{-3} mol litre^{-1} reflects par-

<table>
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<th>Table I. Mean (SEM) ketamine EC_{50} values</th>
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<tr>
<td>Histamine (n = 7)</td>
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<tr>
<td>Acetylcholine (n = 5)</td>
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<td>Barium chloride (n = 5)</td>
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<td>Potassium chloride (n = 3)</td>
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FIG. 1. Relaxation of acetylcholine-contracted bronchial smooth muscle (n = 5).

FIG. 2. Relaxation of histamine-contracted bronchial smooth muscle (n = 7).
tial and non-competitive antagonism. When ketamine $10^{-3}$ mol litre$^{-1}$ was added to the organ bath, it was not possible to generate a dose–response curve to either histamine or acetylcholine.

When ketamine was tested on bronchial preparations pretreated with propranolol 20 µmol litre$^{-1}$ or indomethacin 1.7 µmol litre$^{-1}$, EC$_{50}$ values did not differ significantly from control (table II, fig. 2).

### DISCUSSION

The main findings of this study were that ketamine did not influence the basal tone of human bronchial preparations; antagonized bronchial contraction produced by all the agonists used; and, in all cases, exerted non-competitive and non-specific antagonism. Consequently, it may be concluded that the interactions between ketamine and bronchial tone may result from inhibition of a common pathway leading to contraction.

The mechanisms of bronchial contraction are thought to include: activation of the autonomic nervous system, release of mediators such as prostaglandins, histamine and acetylcholine, and a final common pathway involving calcium supply to contractile proteins. Ketamine has been reported previously to act at each level [3, 5, 6]. The sympathomimetic effect of ketamine has been attributed to potentiation of endogenously released catecholamines, central sympathetic stimulation or inhibition of uptake processes [7].

Abolition by β-block of the bronchodilator effect of ketamine in an *in vivo* model [2] appears to contradict studies *in vitro* [3]. This apparent discrepancy may be explained by release of both systemic and central catecholamines induced by ketamine *in vivo*. Furthermore, in rabbits with denervated sinus and aortic baroreceptors, ketamine has been reported to decrease heart rate, mean arterial pressure and cardiac output [8], suggesting a specific direct effect. However, in our study, propranolol did not inhibit the effect of ketamine, which excludes β-receptor activation.
Indomethacin did not affect the actions of ketamine, excluding a putative role for endogenous prostaglandins.

A potent anti-cholinergic effect has been attributed to ketamine and this may be responsible for part of the bronchodilator action [9]. More recently, the interactions between ketamine, barium chloride and calcium chloride have been studied in isolated guineapig pulmonary arteries [6]; ketamine caused a rightward shift in the dose–response curve to calcium chloride, thus exhibiting a calcium channel blocking property. The mechanism suggested was a dose-dependent inhibition of extracellular calcium transport, which may explain the non-specific antagonism observed. In our study, the relaxation induced by ketamine on barium chloride- and potassium chloride-contracted preparations also suggests calcium antagonism.

Membrane-stabilizing agents, including local anaesthetics [10], generally exhibit a lack of influence on basal tone and non-specific inhibition of contractile agents, including calcium activators.

Ketamine has been reported to produce nerve block by spinal, extradural and i.v. routes [11, 12].

All these findings suggest strongly that ketamine has local anaesthetic properties; this view is consistent with various effects described in the literature and with the results observed in this study.

REFERENCES

10. Low PS, Lloyd DH, Stein TM, Rogers JA. Calcium displacement by local anaesthetics. Journal of Biology and Chemistry 1979; 254: 4119.