TRACHEAL SMOOTH MUSCLE RELAXANT EFFECT OF KETAMINE

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SUMMARY

Ketamine is claimed to decrease airways resistance in patients suffering from bronchoconstriction. Investigations of its mechanism of action were undertaken using the guineapig tracheal chain, a preparation which reacts to drugs in a manner similar to that of the smooth muscle of human bronchioles. Ketamine was found to possess a direct relaxant effect on the tracheal chain, to antagonize the spasmodic effects of carbachol and potentiate the antispasmodic effects of adrenaline. Reduction in airway resistance after ketamine anaesthesia is probably the result of a direct relaxant effect on bronchial smooth muscle and a changed response to endogenous humoral substances.

Ketamine, 2-(0-chlorophenyl)-2-(methylamino)cyclohexanone, was reported by Huber et al. (1972) to decrease airway resistance significantly in patients suffering from bronchospasm. Another clinical advantage of the drug was the finding of Corssen et al. (1972) that asthmatic attacks were not precipitated in patients with a history of asthma and that ketamine abolished or reduced asthma during the acute phase of the attack. The mechanism by which ketamine produces these effects is unknown but it may involve a direct depressant action on bronchial smooth muscle similar to that found previously for this drug on other smooth muscle preparations (Lundy, Colhoun and Gowdey, 1971, 1972, 1973). A search for the beneficial effects of ketamine should include a study of its effects not only on bronchial smooth muscle but also on the interaction of the drug in the presence of other agents known to affect bronchial smooth muscle.

We have studied the effects of ketamine on the guineapig tracheal chain preparation which was chosen because of its similarity in pharmacological response to human bronchiolar tissue (Guirgis, 1969).

METHODS

Following decapitation, the trachea of the young adult male guineapig was removed, placed in Tyrode's solution, cleaned of attached tissue, and cut into individual rings according to the method of Castillo and DeBeer (1947). The rings were tied together with surgical silk to form a chain which was suspended in Tyrode's solution at 37°C through which was bubbled a mixture of 5% carbon dioxide in oxygen. The activity of the tracheal chain preparation was recorded by the combined use of an auxotonic lever, a Harvard smooth muscle transducer and a Rikadenki two-channel linear recorder. In some experiments carbachol (1.5 x 10⁻⁷M) was added to the Tyrode's solution to increase the tone and to facilitate the return of the muscle preparation to the baseline.

Doses of drugs are given in the captions for figures 1–4. Ketamine was used as the hydrochloride and concentrations of adrenaline are given as the base; both drugs were left in the muscle bath for 5 minutes. In experiments where ketamine and adrenaline were used in sequence, ketamine was placed in the muscle bath 30 seconds before the addition of adrenaline. Muscle exposure to the drugs was 5 minutes and in these experiments no attempt was made to randomize the drug sequence. In figures 1 and 4 results for the y axis are given as a percentage of the largest relaxation obtained after a supramaximal concentration of adrenaline. The x axis represents the log dose (base 10) of the drug. In figures 2 and 3, the y axis denotes the actual pen recording of tracheal chain relaxation; the x axis represents the dose of drug used. At least four experiments were carried out to obtain the values given in the figures and where necessary the standard error of the mean (s.e.m.) is shown. The guineapig tracheal chain appears to be a stable preparation; in the experiments reported below all of the bioassays were carried out for periods of no less than 12 hours. The sensitivity of the tracheal chains was checked periodically by determining the response to adrenaline.

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RESULTS

Relaxation of the guineapig tracheal chain in response to ketamine, and ketamine in the presence of carbachol is illustrated in figure 1. Relaxation of the muscle occurred in a dose-related manner. The increased sensitivity of the carbachol-stimulated muscle to ketamine suggests that the drug would have a greater relaxant effect on bronchioles with increased cholinergic tone. The two curves are significantly different (P<0.05) from each other and the ED50 for ketamine relaxation in the presence of carbachol is 2.2 times less than that for ketamine on the normal preparation.

The results in figure 2 show the comparative relaxant effects of ketamine and adrenaline on the tracheal chain in the presence of carbachol, and the effect of these drugs when propranolol (2x10^-5 M) was added to the organ bath. The tracheal chain was approximately 1000 times more sensitive to adrenaline than to ketamine. Moreover, propranolol blocked the relaxant effect of adrenaline but not that of ketamine.

Figure 3 shows a potentiating effect of ketamine on adrenaline-induced relaxation of the tracheal chain. The combination of a subthreshold dose of ketamine 30 sec before the administration of adrenaline produced a response which was much greater than that with adrenaline alone. After washout of the drug combination the response to adrenaline was similar to the initial relaxation before ketamine.

Dose response curves for the relaxation effect of adrenaline and adrenaline in the presence of a subthreshold dose of ketamine (5 µg/ml) are given in figure 4. The relaxation of the tracheal chain to adrenaline was increased twofold when ketamine
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FIG. 3. Effect of a small dose of adrenaline (A, 35 ng/ml) and a subthreshold dose of ketamine (K, 5 µg/ml) on the relaxation of an individual guineapig tracheal chain. K + A represents the same doses of adrenaline and ketamine and shows the potentiating effect of ketamine on adrenaline-induced relaxation.

was added to the organ bath 30 sec before adrenaline. These results together with those given in figure 1 for the carbachol-treated tracheal chain tend to show a non-specific relaxant effect of ketamine in the presence of a spasmogen or an antispasmodic.

DISCUSSION

Huber et al. (1972) and Corssen et al. (1972) have reported that ketamine may be a particularly useful anaesthetic agent in patients suffering from bronchoconstriction because it can reduce airways resistance. The mechanism of action of the decreased airways resistance resulting from the administration of ketamine is unknown but these authors suggest that it may be the result of increased levels of circulating catecholamines.

The experiments reported here may help to explain the beneficial effects of ketamine observed in patients with asthma or other bronchoconstrictive disease. Ketamine has been shown (fig. 1) to relax the isolated tracheal muscle preparation. This finding is similar to the smooth muscle relaxant effects of ketamine which we found previously in studies of the rat stomach strip, chick rectum and rabbit aorta (Lundy, Colhoun and Gowdey, 1971, 1972, 1973).

The failure of propranolol to block the relaxant effect of ketamine suggests that ketamine has no effect on beta receptors. Furthermore, we have other unpublished results which show that ketamine reduces the contraction of the guineapig ileum preparation to acetylcholine, histamine and barium chloride. The mechanism of action of ketamine on smooth muscle in general and bronchial smooth muscle in particular is unknown but it appears to be a non-specific effect at the membrane level. Indeed the recent results of Cronnelly et al. (1973), showing the desensitization of the myoneural junction to acetylcholine by ketamine, support this view.

The present results show that tracheal chains bathed in carbachol and thus in a state of contraction, relaxed comparatively more to ketamine than did those without artificial tone. Furthermore, a subthreshold dose of ketamine potentiated the effect of adrenaline on the tracheal muscle about twofold. It is well established (Widdicombe and Sterling, 1970) that bronchiolar smooth muscle is under vagal control and that the bronchiolar smooth muscle of asthmatics is hypersensitive to spasmogens such as acetylcholine (Makino, 1966). The increased response to ketamine of tracheal chains contracted with carbachol suggests the possibility that patients with constricted airways may also be more sensitive to the relaxant effect of ketamine. With the intravenous doses of ketamine used for clinical anaesthesia, blood concentrations of ketamine could reach levels in the same general range as those used in in-vitro experiments.

There is evidence (Bovill et al., 1971; Lundy, Colhoun and Gowdey, 1973) to suggest that ketamine may increase the level of circulating catecholamines following its injection to produce anaesthesia. This increase, together with the potentiating effect of ketamine to adrenaline on bronchial smooth muscle, may be another important factor which
would help to explain the ability of ketamine to relax bronchial smooth muscle.

Thus three mechanisms may be involved in the effects of ketamine on bronchoconstriction: a direct depressant effect on the smooth muscle, a potentiation of the relaxant effect of adrenaline, and increased levels of circulating catecholamines.

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REFERENCES


