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Ketamine and its isomers have equipotent relaxant effects on tracheal smooth muscle contracted by tachykinins

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Abstract: Recent studies indicate that not only inflammatory cells but also neural mechanisms by which tachykinins such as substance P (SP) and neurokinin A (NKA) are released from vagal afferent C-fiber contribute to asthma. Although ketamine (K) has been used in the anesthetic management of asthmatic patients, the mechanism by which K relaxes the airway smooth muscle is still uncertain, and no information exists on any differential effect of K and its isomers. We determined the spasmolytic effect of racemic [R(±)] K and its isomers S(+) K and R(−) K on SP and NKA-induced contraction of tracheal smooth muscle in guinea pigs. Strips of guinea pig trachea were mounted in an organ bath filled with Tyrode's solution at 37°C bubbled with 95% O_2/5% CO_2. Strip tension was measured isometrically with a force displacement transducer. Strip contraction was elicited with SP 10^{-6}M or NKA 5×10^{-7}M. R(±), R(−), or S(+) K ($4.5–18.0 \times 10^{-4}$M) was cumulatively administered into the bath. The calculated ED_{50} values (the concentration that relaxed the contraction by 50%) of R(±), R(−), and S(+) K were 7.6 ± 0.5, 7.8 ± 0.6, and 7.6 ± 0.5 (10^{-4}M), respectively, when the contraction was elicited with SP, and 8.0 ± 1.0, 8.2 ± 1.2, and 7.9 ± 1.3 (10^{-4}M), respectively, when NKA was used. We concluded that K and its isomers have equipotent spasmolytic effects on airway smooth muscle precontracted with tachykinins.

Key words: Ketamine, Airway smooth muscle, Tachykinin, Asthma, Bronchoconstriction

Introduction

Asthma is classified as an inflammatory disease because inflammatory changes have been observed in airways of asthmatic patients, even in the mildest form of the disease [1,2]. Recent studies indicate that not only inflammatory cells with their mediators but also the neuronal mechanism may contribute to asthma [3]. Neurogenic inflammation in asthma may be caused by antidromic releases of neuropeptides from vagal afferent c-fiber by way of an axon reflex [4]. In particular, tachykinins such as substance P (SP) and neurokinin A (NKA) bring about many of the pathophysiologic features of asthma, such as bronchoconstriction, increase in vascular permeability, and mucus secretion [5,6].

As ketamine (K) is known to have a potent bronchodilating effect [7–10], it has been used in the anesthetic management and the treatment of asthmatic patients [11–14]. Many pharmacological differences between optical isomers of K have been reported [15–17]. However, very little is known about the spasmolytic effect of K and its isomers on tachykinins-induced contraction of the airway smooth muscle.

Methods

Our study protocol was approved by the Animal Care and Use Committee at the University of Illinois at Chicago.

Guinea pig tracheal strip

Female guinea pigs were killed with an overdose of IP pentobarbital (75 mg·kg^{-1}) and the abdominal aorta was sectioned. The trachea was removed, isolated from surrounding tissue, and cut spirally into strips 3 mm wide and 15 mm long. The strips were mounted in a 10-ml organ bath filled with Tyrode's solution at 37°C, which was bubbled with 95% O_2/5% CO_2. The composition of Tyrode's solution was (in mM): NaCl, 138; KCl, 2.7; $MgCl_2$, 1.05; $NaHPO_2$, 0.42; $NaHCO_3$, 11.9; glucose, 5.5; $CaCl_2$, 1.8. Each strip was stretched between a fixed point and a force-displacement transducer (FT03,

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Grass Instruments, Quincy, MA, USA). Experiments were begun after reproducible contractions by SP (10^{-6}M) or NKA (5×10^{-7}M) were obtained. The three forms of K, racemic [R(±)], S(+), or R(−), were tested in the same tracheal strip in a randomly determined order. Each contraction by SP or NKA was elicited 10 min after washing the strip with Tyrode's solution.

The experimental protocol was designed to determine the relaxant effect of K and its isomers on the tone of tracheal strips precontracted with SP ($n = 6$) or NKA ($n = 6$). Following the maximal contraction, R(±), S(+), or R(−) K was cumulatively given to obtain concentrations in the bath of 0.45×10^{-3}M, 0.9×10^{-3}M, and 1.8×10^{-3}M for each K form. The relaxation was expressed as a percentage of the peak contraction (0) to the baseline (100%). The ED_{50} values (the dose of K or its isomers that reversed tachykinin-induced contraction by 50%) were calculated from the concentration-response curve.

Data analysis

Results are expressed as mean ± SEM. Statistical analysis was done with one-way ANOVA followed by the Scheffe F-test. A $P < 0.05$ was considered significant.

Drugs and solutions

Racemic K hydrochloride, SP, and NKA were obtained from Sigma Chemicals (St. Louis, MO, USA). Sodium pentobarbital was purchased from Abbott Laboratories (North Chicago, IL, USA). S(+) and R(−) K hydrochloride were generously donated by Parke, Davis (Munich, Germany).

Stock solutions of R(±), S(+), and R(−) K were prepared in distilled water. All stock solution were stored in aliquots at −20°C.

Results

SP 10^{-6}M and NKA 5×10^{-7}M increased basal tension of the tracheal strips by 0.57 ± 0.06 and 1.23 ± 0.17 g, respectively.

After precontraction of the strips with SP or NKA, R(±), R(−), and S(+) K relaxed the tracheal strips in a concentration-dependent manner (Fig. 1). There was no significant difference among the ED_{50} values of R(±), R(−), and S(+) K, which were 7.6 ± 0.5, 7.8 ± 0.6, and 7.6 ± 0.5 (10^{-4}M) SP and 8.0 ± 1.0, 8.2 ± 1.2, and 7.9 ± 1.3 (10^{-4}M) in NKA, respectively. This relaxing effect of K and its isomers was fully reversible upon washing.

Discussion

Many investigators have used histamine as an airway constrictor in both in vivo and in vitro studies of the spasmolytic effect of K [7,9,10]. However, asthma is considered to result from the action of not only histamine, but also many other inflammatory mediators such as tachykinins, bradykinin, prostaglandins, and cytokinins [3]. As K is known to produce bronchodilation even in asthmatic patients who do not respond to conventional therapies [12–14], it may inhibit the contraction of airway smooth muscle induced by the inflammatory mediators which are known to contribute to the pathophysiology of asthma.

Our present data indicating that K and its isomers can inhibit the contraction of tracheal smooth muscle induced by tachykinins are consistent with our previous finding in guinea pig ileum [18]. In the ileum smooth muscle, we found that K and its isomers equipotently inhibit the contractions induced by histamine, serotonin, bradykinin, NKA, and SP [18]. In the present study, we consistently observed that all three forms of K have equipotent relaxant effects on tachykinins-induced contraction of tracheal smooth muscle.

Although the ED_{50} of K (8.0×10^{-4}M) in the present study was higher than the clinically relevant serum con-

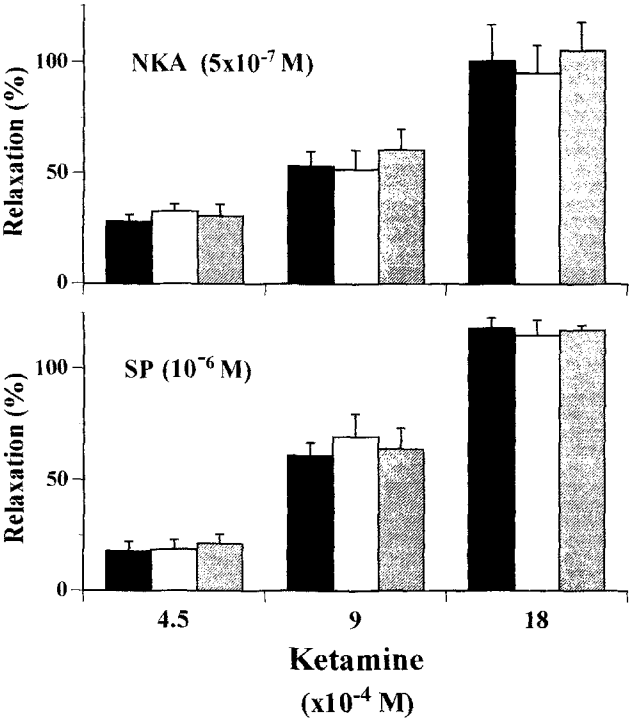

Fig. 1. Relaxant effect of R(±), S(+), and R(−) ketamine (K) on substance P (*SP*) and neurokinin A (*NKA*)-induced tracheal contraction. No significant differences in the effect was found among the three forms of K. All values are presented as mean ± SEM. *Black, white and shaded columns* represent R(−), R(±), and S(+) K, respectively

centration (2×10^{-5}M) [19], Cheng et al. [20] showed that K could produce a greater relaxation on the distal airway than on the proximal one. Therefore, the clinical concentration might produce more than 50% relaxation of the tachykinins-precontracted distal airway, which is more important in regulation of airflow resistance than the proximal one [21,22].

S(+) K is known to produce more potent anesthetic effects and less psychic emergence reactions in the postanesthetic period than R(−) K [15]. Moreover, as we reported that S(+) K could significantly reduce vascular permeability in chemical peritonitis while R(−) K did not [17], S(+) K may attenuate not only the contraction of airway smooth muscle but also the airway edema in patients with asthmatic attack. Therefore, S(+) K could be more valuable in clinical use for asthmatic patients.

In conclusion, we have found that K and its isomers can relax the airway smooth muscle precontracted by tachykinins, and that there is no significant difference among R(±), R(−), and S(+) K in their ability to do so.

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