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Original Article

Vardenafil inhibiting parasympathetic function of tracheal smooth muscle

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Abstract

Background: Levitra, a phosphodiesterase-5 (PDE5) inhibitor, is the trade name of vardenafil. Nowadays, it is applied to treatment of erectile dysfunction. PDE5 inhibitors are employed to induce dilatation of the vascular smooth muscle. The effect of Levitra on impotency is well known; however, its effect on the tracheal smooth muscle has rarely been explored. When administered for sexual symptoms via oral intake or inhalation, Levitra might affect the trachea.

Methods: This study assessed the effects of Levitra on isolated rat tracheal smooth muscle by examining its effect on resting tension of tracheal smooth muscle, contraction caused by 10^{-6} M methacholine as a parasympathetic mimetic, and electrically induced tracheal smooth muscle contractions.

Results: The results showed that adding methacholine to the incubation medium caused the trachea to contract in a dose-dependent manner. Addition of Levitra at doses of 10^{-5} M or above elicited a significant relaxation response to 10^{-6} M methacholine-induced contraction. Levitra could inhibit electrical field stimulation-induced spike contraction. It alone had minimal effect on the basal tension of the trachea as the concentration increased.

Conclusion: High concentrations of Levitra could inhibit parasympathetic function of the trachea. Levitra when administered via oral intake might reduce asthma attacks in impotent patients because it might inhibit parasympathetic function and reduce methacholine-induced contraction of the tracheal smooth muscle.

Keywords: *In vitro* study; Smooth muscle; Trachea; Vardenafil

1. Introduction

The enzyme phosphodiesterase-5 (PDE5) is known to be abundant in lung tissue where it hydrolyses cyclic guanosine monophosphate (cGMP), a second messenger of NO, causing constriction of the blood vessel walls.[1] Four PDE5 inhibitors namely sildenafil, tadalafil, vardenafil and avanafil have been clinically approved for treating erectile dysfunction (ED).[2] They are also employed to induce dilatation of the vascular smooth muscle and to inhibit platelet aggregation in treating testicular torsion, pulmonary hypertension, coronary artery disease, diabetes mellitus, chronic peripheral arterial diseases, ischemic colitis and acute mountain sickness.[3−9] There should be particular caution when prescribing PDE5 inhibitors for erectile dysfunction in patients receiving protease inhibitors. PDE5 inhibitors appear to work in men regardless of the reasons behind their erectile dysfunction, including vascular disease, nerve problems, and even psychological causes. PDE5-inhibiting drugs can have a number of side effects, including headache, dizziness,

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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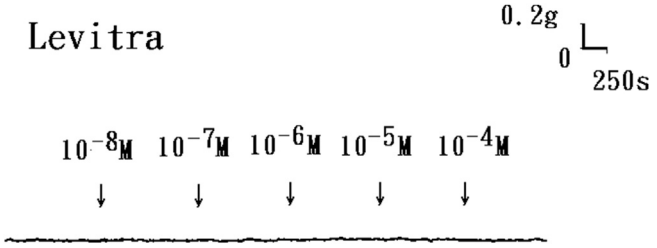

Fig. 1. Tension changes in rat trachea after application of various Levitra concentrations. Levitra alone had minimal effect on the basal tension of trachea as the concentration increased. Original basal tension was 0.3 g.

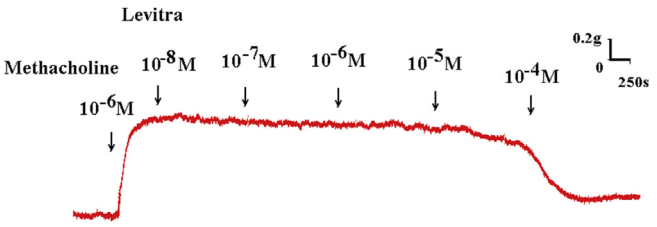

Fig. 2. Original recording of the effects of Levitra on 10^{-6} M methacholine-induced contraction of rat trachea.

lightheadedness, flushing, nasal congestion, and changes in vision.[10] (see Figs. 1–5)

Levitra is the trade name of vardenafil. It has been used as a PDE5 inhibitor to treat ED for a decade.[2] The side effects of PDE5 inhibitors had been reported but their effect on the trachea was rarely mentioned. During an asthma attack, the tracheal smooth muscle becomes contracted, thus reducing pulmonary function. A male patient with asthma may also apply this drug via oral intake or inhalation for his sexual problems. Hence, the effect of Levitra on tracheal smooth muscle merits further exploration. The aim of this study was to determine the effects of Levitra on the isolated tracheal smooth muscle *in vitro*.

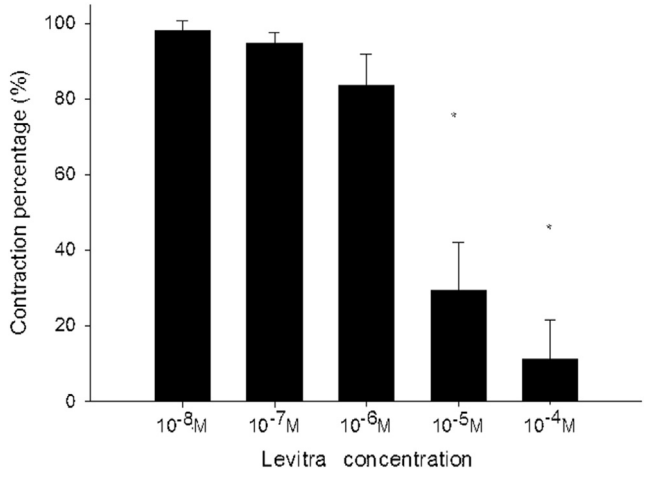

Fig. 3. Effects of Levitra on 10^{-6} M methacholine-induced contraction (contraction area calculated at 100% without addition of Levitra) of rat trachea. The difference in tension between 10^{-8} M Levitra and 10^{-5} M Levitra or 10^{-4} M Levitra was statistically significant ($p < 0.05$). Results were mean ± SD (n = 6).

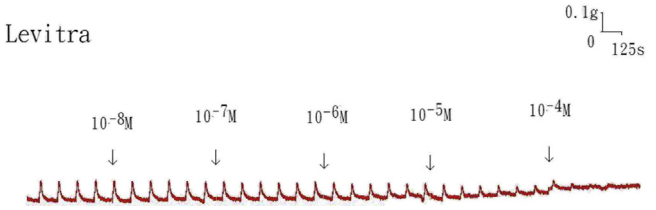

Fig. 4. Original recording of effects of Levitra on electrically induced tracheal smooth muscle contractions was noted. Higher doses of Levitra also decreased the spike contraction induced by EFS.

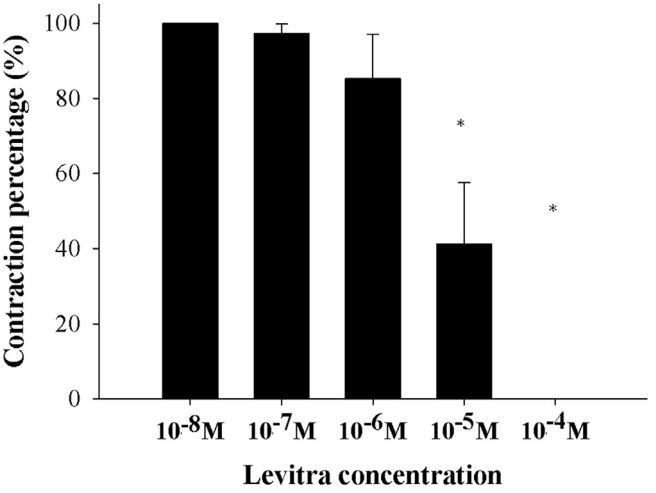

Fig. 5. Effects of Levitra on electrically induced tracheal smooth muscle contractions (contraction area calculated at 100% without addition of Levitra). The peak tension of the tracheal strip evoked by EFS during the addition of 10^{-4} M Levitra was significantly lower than that at the addition of 10^{-8} M Levitra ($p < 0.001$). Results were mean ± SD (n = 6).

2. Methods

Chemicals used were of the highest purity available. Levitra was obtained courtesy of Bayer Co., Taiwan. All other chemical reagents were obtained from Sigma (St. Louis, MO, USA). Methacholine was tested as a tracheal contraction drug. After being anesthetized by intraperitoneal administration of pentobarbital (45 mg/kg), 18 male Sprague–Dawley rats (weighing 250–300 g) were humanely killed by cervical dislocation, and two pieces of trachea (~5 mm in length) were removed from each rat. This study was approved by an animal experiment review board (IACUC-07-133). The tracheal specimen was mounted using two steel plates and submersed in a 30-mL muscle bath at 37 °C as previously reported.[11,12] Briefly, the bath was filled with 30 mL Krebs solution consisting of (mmol/L): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; and glucose, 10.0. Levitra was dissolved in dimethylsulphoxide (DMSO) and subsequently diluted in Krebs solution. Our preliminary *in vitro* studies showed that the vehicle (diluted DMSO) had no effect on the rat tracheal smooth muscle. The upper side of the

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