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The Mechanisms of Ephedrine Suppressing Fentanyl-Induced Cough

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ABSTRACT. *Ephedra, as traditional Chinese medicine, is often used to treat diseases such as cough and pneumonia as the main component of it is ephedrine, which is proved can prevent fentanyl-induced coughing. Ephedrine intravenous injection is widely used in traditional Chinese medicine. It can soothe the smooth muscles of the trachea, but the mechanism is unclear. Exploring the inhibitory mechanism of this may lay a foundation for ephedrine to act on similar symptoms.*

KEYWORDS: *Ephedrine, Fentanyl-induced cough, Muscle contraction*

1. Introduction

Fentanyl, a synthetic opioid, is widely used for general anesthesia during operations with the features of fast and strong action and a short duration of a single administration. However, sometimes patients will develop a cough after injection. In Bohrer's report, 46% of patients had a reported fentanyl-induced cough after being delivered 7μg/kg of fentanyl through a central venous catheter. [1] The phenomenon is unexpected in patients with co-existing diseases, including intracranial pressure and pneumothorax. It is necessary to prevent fentanyl-induced cough.

There are three hypotheses proposed for the mechanism of fentanyl-induced cough. Paintal et al. [2]and Yasuda et al. [3] proposed a pulmonary chemoreflex which was mediated by either irritant receptors or vagal C-fiber receptors. Once these receptors are stimulated by fentanyl, sudden bronchoconstriction and coughing will be triggered. Substances released by action on the prejunctional μ-opioid receptors play an important role in causing cough.[4][5][6] In another research, Benthuysen et al.[7] argued that vocal cord spasms may induce cough. Whatever the mechanism of fentanyl-induced cough is, the result is the activation of nerves near the trachea and the contraction of smooth muscle of the trachea. The contraction of muscle is caused by an opening of the sodium-potassium pump pathway and Na+ flowing into cells. K+ can also cause it. So, adding high concentration K+ is to simulate the contraction of tracheal smooth muscle.

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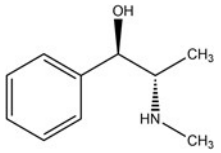

Ephedrine may suppress cough by reversing the fentanyl-triggered bronchoconstriction.[8] Its relaxing bronchial function is recognized by scientists. Since the mechanism is not precise, the time and duration of efficacy of intravenous ephedrine and oral ephedrine water extract remain to be studied.

2. Methods

The experiment used the trachea of mice as samples. The isolated tissue was placed in a pre-cooled rTAS solution and isolated the tracheal smooth muscle. Removing connective and adipose tissue from both sides of the trachea. We took 5mm long trachea and connected to the tension transducer. PSS solution was exchanged every 15min. 60min later, the trachea ring was placed in water bath at a constant temperature of 37℃, set preload as 300mg, and 80mM KCl was used to do pre-stimulation three times. The experiment started after the tissue has relaxed for 30min. The treatment of samples is shown in table 1. For each sample, the tension transducer image was collected and used to analyze the contraction of the trachea ring.

Sample 1: Adding 80mM KCl to the buffer solution to induce stable contraction of the tracheal ring of mice. 20min later, 0.316~316μM ephedrine was added cumulatively to a water bath with a trachea ring suspended in it. (Figure 1-1)

Sample 2: Adding 100μM ephedrine into the buffer solution when the tracheal ring was at resting state. (Figure 1-2)

Sample 3: Adding 80mM KCl. 20min later, adding 10μM nifedipine into the buffer solution to block the muscle conduction induced by K+. (Figure 1-3)

Sample 4: Placing the tracheal ring in the buffer solution without Ca2+and added 8-mM KCl. After 5min, restoring the Ca2+ concentration to 2μM. When the tracheal ring was induced to have stable contraction, adding 100μM ephedrine into the buffer solution. (Figure 1-4)

Sample 5: Placing the tracheal ring in a buffer solution without Ca2+, adding 100μM ephedrine into the buffer solution before KCl. Then restoring the Ca2+ concentration to 2μM. (Figure 1-5)

Sample 6: Adding 100mM ACH to the buffer solution. Adding 0.316~316μM ephedrine cumulatively to a water bath with a trachea ring suspended in. (Figure 2-1)

Sample 7: Adding 100mM ACH, adding 10μM nifedipine into the buffer solution,

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and adding 100μM ephedrine 1 minute later. (Figure 2-2)

Sample 8: Placing the tracheal ring without Ca2+, and adding 10μM nifedipine. After one muscle contraction, adding 2mM Ca2+, after 30s, added 300μM ephedrine. (Figure 2-3)

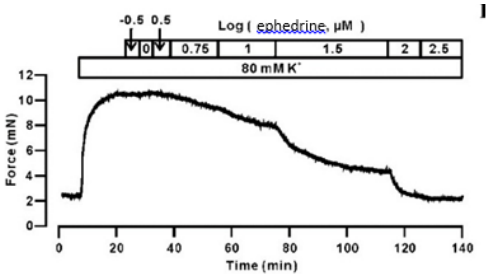

Figure 1-1

Figure 1-1: As the ephedrine was cumulatively added, the contraction level of tracheal ring gradually drops to the pre-contraction level.

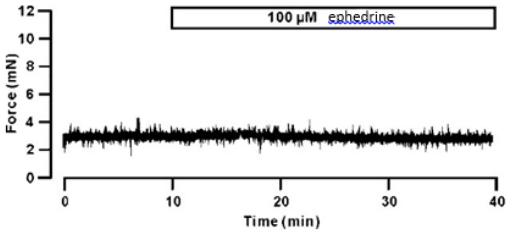

Figure 1- 2

Figure 1-2: The ephedrine could not change the contraction force of the tracheal ring in the resting state. But if the tension was lower than that before adding ephedrine, ephedrine can reduce the contraction of the tracheal rings in the resting state, and there may be a kind of inhibitor of muscle contraction.

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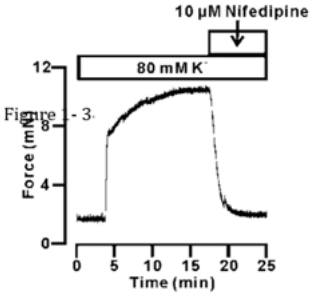

Figure 1-3

Figure 1-3: Nifedipine could effectively block muscle contraction induced by a high concentration of K+. Compared with ephedrine, nifedipine can work in a shorter time.

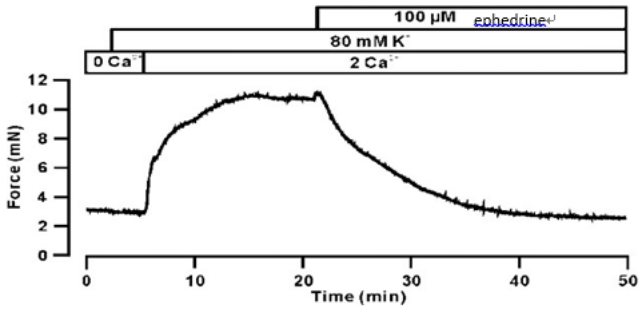

Figure 1-4

Figure 1-4: When replacing the tracheal ring in the buffer solution without Ca2+, there was no contraction, and the K+ concentration is high. Restoring the concentration of Ca2+ induced the contraction. The contraction could be blocked by ephedrine.

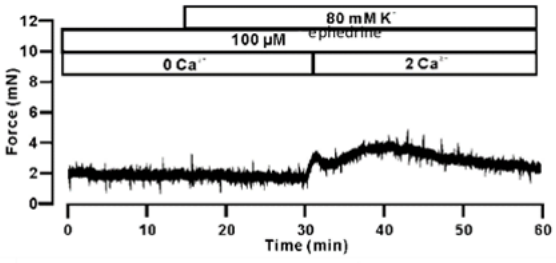

Figure 1-5

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Fig.2 -1: When Adding Ephedrine Before Kcl and Ca2+, the Contraction of the Tracheal ring Was Slight.

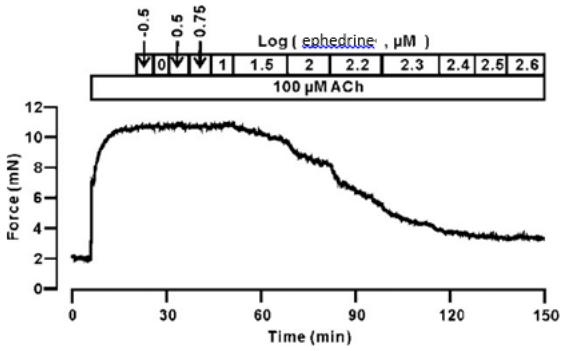

Figure 2-1

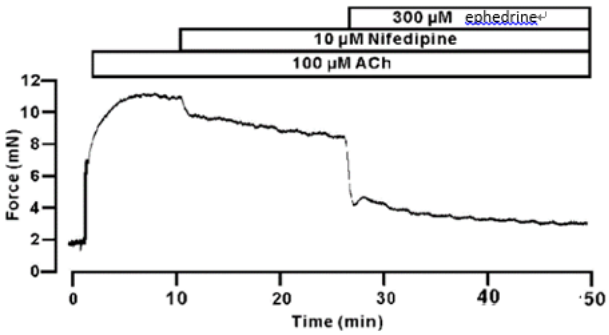

Figure 2-2

Figure 2-2: Ephedrine could influence relaxation of muscle contraction induced by ACH.

After the tracheal ring contraction induced by ACH, nifedipine could partly relax the contraction, and the rest can be further reduced by ephedrine. This meant that ephedrine did not serve totally the same as nifedipine did. If the contraction did not change after adding ephedrine, ephedrine and nifedipine had the same function to reduce the contraction.

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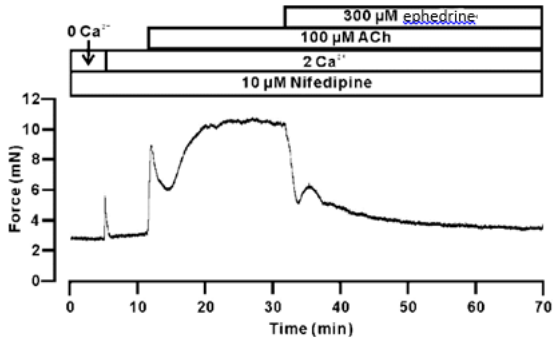

Figure 2-3.

Figure 2-3: There was a contraction with the nifedipine, which means Ca2+ had already flowed out of the cells. When restoring the concentration of Ca2+, there was a stable contraction that can be blocked by 300μM ephedrine.

3. Conclusions

Scientists have found that a high concentration of K+ can cause polarization of cell membrane and activate the VDLCCs pathway. Ca2+ outside the cells is promoted to flow into the cells. Finally, there is a tracheal ring contraction. Figure 1-1 to 1-4, ephedrine reduces the contraction of the tracheal ring, which is induced by high concentration K+ through blocking VDLCCs pathway. Figure 1-5 showed that ephedrine blocks VDLCCs pathway by suppressing Ca2+ flow into cells.

In figure 2-1, after the tracheal ring contraction which is induced by ACH, nifedipine, can partly relax the contraction. This means ephedrine reduces the contraction, which is induced by ACH through VDLCCs and an unknown pathway.

Based on figure 2-3, we inferred that the pathway, in which nifedipine tolerant and Ca2+ flow into cells, is the NSCCs pathway. The figures above show one possibility of the results.

The experiment should be repeated more times to ensure that the results are valid.This study only works on the mechanisms of ephedrine served as a bronchodilator to suppress the fentanyl-induced cough. It is also beneficial to cure asthma or other tracheal diseases. Injection of ephedrine brings us a new idea of the application of traditional Chinese medicine. Extracting active ingredient in Chinese medicine is essential to the improvement of clinical application. Using steam distillation and solution extraction to extract and purify ephedrine from ephedra is time-consuming, and the purity is low. How to extract ephedrine from ephedra economically and efficiently will be a research trend.

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