Pharmacologic Effects of Nicotine on Isolated Aorta, Trachea and Lung Function of Rat.

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Abstract

Nicotine is one of the most important substances in cigar and the cigarette Smoke. Smoking may cause an increase in blood pressure and affecting respiratory functions. In this study the effect of nicotine on isolated aorta and trachea of rat and also it's effect on the bronchial resistance, was investigated. In the in vitro experiments, trachca or aorta was removed and placed in an isolated tissue organ bath containing Krebs Henseleit solution at pH 7.2-7.4 at 37°C and aerated with 95% O₂ and 5% CO₂. Epineprine (for aorta) and acetylcholine (for trachea) were used as Standard Stimulating agents. They elicit a dose dependent contracture in those tissues. Dose-response curve was established for each drug. Then different concentrations of nicotine solution (10⁻⁸ to 10⁻² M) was tested on either aorta or trachea. Results showed that nicotine with such concentrations can not elicit contraction in isolated rat aorta and trachea. In the in vivo experiments, different doses of drugs were directly nebulized in the rat trachea and their effects on the bronchial resistance were measured. Barium chloride (BACl₂) was used as standard stimulating agent and changes in bronchial resistance was recorded. Epinephrine was used to reverse the bronchospasm induced by BaCb. Then different concentrations of nicotine solution (10⁻⁵ to 10⁻¹ M) was nebulized. According to the results of this study nicotine with these concentrations had no bronchoconstriction effect in rat. Therfore it can be concluodned that nicotine alone has no direct effect on isolated banchia, aorta or bronchial resistance. However its adverse effect on human health may be due to other adjuant ingredients in cigarette smoke.

Introduction

Tobacco (Nicotiana tabacum) is an annual plant that belongs to solanaceae family. It's height is 3-10 feet, and it's flowers are pink and hermaphrodite. The plant originates from tropical America and is cultivated in many countries such as U.S.A., China, Turkey, Iran, Greece, Holland, France, Germany and most subtropical countries (1). The whole of this plant, specially, the leaves contains nicotine. There are about 4000-5000 different substances in the cigarette smoke and about half of them are related to tobacco leaves (2).

Tobacco smoke contains two phases:
1. Gas phase: This phase is invisible and contains some gases and vapours such as: CO₂, CO, NH₃, HCOH, HCN, ...
2. Particular phase: This phase is the smoke that we can see, and contains the small unburned particles such as: water, alkanes, organic acids, alcohols, Nicotine, tar,... (3,4)

The harmful effects of cigarette on different parts of human body may cause Cancer; specially lung cancer. Cardiovascular diseases such as increased blood pressure. Respiratory problems: specially Chronic Obstructive Pulmonary Diseases (COPD) (5).

Nicotine: Nicotine is a colorless base that in vicinity of the air becomes brown. It dissolves freely in water, alcohol and ether. It’s amount in tobacco leaves is 2-8%. The signs of poisoning with Nicotine are: nausea, vomiting, diarrhea, sweating, weakness of skeletal muscles, fluctuation of blood pressure and heart beat, heart attack and finally respiratory depression. Lethal dose of Nicotine is 40-100mg for adults (1).

Since cigarette smoking causes an increase in blood pressure and respiratory problems, we decided to examine the direct effect of nicotine on contractility of smooth muscles in aorta and trachea of rat.

Materials and Methods

In this study, Wistar albino rats of either sexes, weighing 175-220g were used. They were housed in standard cages at a 12hr cycle of light and dark. Room temperature was kept at 23±2°C and humidity maintained at 50%. Rats were allowed to become acclimatized to standard laboratory condition for at least 5 days and standard food and water was provided ad libitum.

In vitro experiments (Isolated aorta and trachea preparations):
The animals were killed by ketamine over-dose (80mg/kg), trachea and desending aorta were removed within 3 min of death. The animal tissues were manually trimmed to remove connectiveand other tissues. Single piece of trachea (1cm) was cut
and then it was cut spirally to provide smooth muscles in one direction. Tracheal spiral was suspended in a 20ml organchamber containing Krebs-Hanseliet buffer of the following composition: NaCl, 11mmol/l; KCl, 4.80mmol/l; CaCl2, 2.35mmol/l; MgSO4, 1.20 mmol/l; KHPO4, 1.2mmol/l; NaHCO3, 25mmol/l; dextrose, 11 mmol/l; and Na2 ethylenediamine tetraacetic acid, 0.03mmol/l, in distilled water. Organ chamber was maintained at 36.5 ± 0.5°C and were continuously aerated with 95% oxygen and 5% carbon dioxide to maintain pH 7.2 to 7.4. Aorta was cut into rings of 5mm length then each ring was placed between two L-shaped stainless steel hooks mounted in sloated organ bath preparation.

Both tracheal spiral and aorta ring were initially set to 2g tension, and were allowed to stabilize for approximately 1.5 h before the experiment began. During the period of stabilization, the tissue was washed at 15-min intervals. After the relaxation period, the tension in each tissue was readjusted to 2g for all subsequent assays. Isometric contractions were recorded using a UF1 force displacement transducer attached to a Harvard polygraph recorder.

Control experiments:
In these experiments, in order to assure of tissue function, epinephrine (1 mM) for aorta, and acetylcholine (10-4 M) for trachea, was added into the organ bath. That doses caused the tissues to contract.

Test experiments:
a) on isolated aorta:
In these experiments different concentration of epinephrine (5×10-9 – 10-4M) was tested on isolated aorta and dose-response graph was established. (graph 1)
Then different concentrations of Nicotine (10-8 –10-2M), was tested on that preparation. However no contraction was elicited by nicotine.

b) on isolated trachea:
Different concentrations of acetylcholine (10-8 –10-3 M) were tested on isolated trachea and dose-response curve was established. Then different concentrations of nicotine (10-8–10-2 M) was tested on tracheal preparation. However no contraction was elicited by nicotine.

Invivo experiments (study the effect of Nicotine on bronchial resistance of rat):
In these experiments, the animals became anesthetized by ketamine (50 mg/kg). Then the muscles of neck and some part of thorax were split vertically, until trachea became clear. A small incision was made on trachea and then respirator (Harvard Aparatus, England) was connected to the trachea in order to maintain the respiratory function of animal(fig 5). The bronchial resistance were measured using a pressure transducer previously connected to the expiratory tube of the respirator (fig 1). As a standard stimulating agent, 1 ml of BaCl2 solution (150mg/ml) was nebulized via a nebulizer which was connected to the respirator. In order to reverse the barium chloride-induced bronchospasm 1ml of epinephrine solution (1mg/ml) was bebulised. Then the effect of nebulised nicotine (10-5 to 10-1 M) was tested.

Results and Discussion

Results of invitro studies showed that epinephrine could cause a does dependent contraction of isolated aorta but nicotine was not able to elicit any contraction in rat aorta (fig 1). Acetyl choline could cause a does dependent contraction in isolated trachea but nicotine was not able to elicit any contraction in rat aorta (fig 2).

Results of invivo studies verified that barium chloride can induce bronchospasm in lung of rat. The effect of BaCl2 was reversed by epinephrine. Nicotine could not induce bronchoconstriction in rat. (fig 3). These experiments showed that nicotine with these concentrations had no contractile effect in isolated rat aorta and trachea, and also can not elicit bronchoconstriction in rat. Therefore we can conclude that:

1. Since cigarette smoke contains 4000-5000 different chemical substances (2), may be nicotine is not the reason of increased blood pressure and bronchospasm that caused by cigarette smoke; and the other substances in cigarette smoke causes these effects.
2. Although nicotine has no direct effect on isolated rat aorta; but it can affect on sympathetic ganglia and the adrenal gland and cause them to excrete norepinephrine, and thus maybe cause increased blood pressure. Sympathomimetic response to nicotine is also due to activation of chemoreceptors of the aortic and carotid bodies which reflexly can cause vasoconstriction and increase in blood pressure (6).
3. however nicotine had no direct effect on contractility of smooth muscles of rat trachea and bronchial resistance, but it can affect on nAchRs and cause them to excrete acetylcholine, and may be in this manner can cause bronchospasm.

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Illustrations

Illustration 1

Fig 1: Dose response curve of epinephrine on isolated rat aorta. Nicotine had no contractile effect which can be shown in this figure.
Illustration 2

Fig 2: Dose response curve of acetyl choline on rat rat trachea. Nicotine had no contractile effect which can be shown in this figure.
Illustration 3

Fig 3: Sample traces of the effects of BaCl2, ephinephrine and nicotine on bronchial resistance of rat
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