

Communication

Nicotine's Effectiveness in the Isolated Human Nasal Mucosa

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Abstract: Nicotine is a stimulant that affects the ganglia. Similar to capsaicin, it also activates sensory nerves in the airways, which leads to secretion and coughing in human subjects. The nasal mucosa can be exposed to the drug through either nasal or oral administration. The study investigated the effects of nicotine on electrically stimulated contractions of human nasal mucosa, resting tension of human nasal mucosa, and contractions induced by 10^{-6} M norepinephrine (NE) or 10^{-6} M methoxamine, a sympathetic mimetic. The purpose was to assess the direct impact of nicotine on human nasal mucosa in an in vitro laboratory setting. The findings demonstrated that the nasal mucosa contracted in a dose-dependent manner upon the addition of methoxamine to the incubation medium. Addition of nicotine at doses of 10^{-4} M elicited a significant relaxation response to 10^{-6} M methoxamine-induced mucosal strip contraction. Nicotine could inhibit electrical field stimulation-induced spike contraction and had a negligible effect on the basal tension of the nasal mucosa as the concentration increased. Adding 10^{-6} M nicotine to the 10^{-6} M NE-induced contraction, it initially induced a small reduction of the contraction, then it potentiated the contractions. This study demonstrated that high nicotine concentrations had a significant spasmolytic effect via antagonistically binding to α -adrenoceptors. Moreover, people with nasal allergies and stuffy noses who additionally utilize an α -adrenergic agonist nasal spray, oral or smoked nicotine, or both concurrently may not get relief from nasal obstruction.

Keywords: Nicotine; Sympathetic Function; Human Nasal Mucosa; In Vitro Study

1. Introduction

According to the National Adult Tobacco Survey, cigarette smoking among U.S. adults has declined from 42.4% in 1965 to 11.6% in 2022 [1–5]. Although the prevalence rate has declined, cigarette smoking causes more deaths each year than any other preventable cause in the US. Smoking affects nasal obstruction and sleep apnea. Differences in tobacco product use among cancer survivors, specifically between those with smoking-related cancers and those with cancers not related to smoking, necessitate proactive cessation support. Oncologists should consider patients' past and present use of tobacco products, their related beliefs, and any socio-demographic obstacles

to quitting by routinely including customized and comprehensive counseling during standard oncology appointments [6]. After being released into the environment, secondhand cigarette smoke undergoes chemical and physical changes. Thirdhand cigarette smoke is one way that some of the resultant toxins remain indoors. Particles from thirdhand smoke that have been absorbed by surfaces may return to the atmosphere [7–9]. If people stopped smoking, they could reduce their risk of tobacco-related morbidity and mortality and potentially gain up to a decade of life. Both electronic and tobacco cigarettes release nicotine, a sympathomimetic drug. The smoking of tobacco may make nicotine the most widely used inhaled drug. Nicotine is a ganglionic stimulant drug [10]. It induces secretion and coughing in humans by stimulating the sensory innervation of the airways, just like capsaicin does. Nicotine causes mucosal exudation of plasma in the tracheobronchial airways of guinea pigs. It is brought on by stimulating lignocaine-sensitive nerves, most likely those that contain tachykinin. A significant part of the pathogenesis of airway illnesses is played by plasma exudation. Human upper and lower airways include nerves that produce tachykinin. The effectiveness of nicotine in isolated human mucosa has hardly been studied. Its effects on mucosal exudation of plasma and on the epithelial barrier function of human airways are well known [11–14]. The effect of nicotine on the nasal mucosa is an issue worthy of investigation because, during administration of the drug, the nasal mucosa may be affected via nasal inhalation or oral intake. In this study, the effects of nicotine on isolated human nasal mucosa in vitro were investigated by utilizing surgical specimens, which demonstrate the tension change of human nasal mucosa after the addition of sympathetic mimetic agents and electrical field stimulation (EFS) that affect the nasal mucosa directly.

2. Materials and Methods

2.1. Tissue Sampling and Preparation

The purest chemicals on the market were used. The source of the nicotine was Chem Services Ltd. (Vancouver, BC, Canada). Sigma provided other chemical reagents that were used (St. Louis, MO, USA). Nasal mucosal strip preparation was done in vitro [15,16]. Eighteen patients had mucosal specimens taken during elective turbinec-tomies. Hypertrophic rhinitis-related significant nasal blockage was one of the indications for surgery. Tissues were removed under general anesthesia. After surgery, each patient may provide 2 to 4 testing samples. Approximately 48 testing samples were utilized. This preparation's reaction to medications and electrical stimulation has been previously documented [17,18]. After removal, a 5 × 15 mm nasal mucosal strip was attached with two steel plates and placed in a 30 mL muscle bath at 37 °C. Thirty milliliters of Krebs solution (mmol/L) containing the following was added to the bath (**Figure 1**): NaCl, 118; CaCl₂, 2.5; KCl, 4.7; MgSO₄·7H₂O, 1.2; KH₂PO₄, 1.2; NaHCO₃, 25.0; and glucose, 10.0. Following its dissolution in dimethyl sulfoxide (DMSO), nicotine was diluted using Krebs solution. Our initial research indicates that the vehicle, which was diluted DMSO, had no effect on the nasal mucosal strip in vitro studies. The upper side of the nasal mucosal strip was attached to a Grass FT-03 force displacement transducer (AstroMed, West Warwick, RI, USA) using a steel plate and a 3-0 silk ligature. The other end of the strip was secured in place by a steel plate attached to the wall of the bath. A passive tension of 0.5 g was applied to the strips, and the Chart V4.2 program (Power Lab, AD Instruments, Colorado Springs, CO, USA) was used to continually record any changes in tension.

2.2. Methoxamine Test

Methoxamine was investigated as a treatment for contractions of the mucosa. Preliminary testing revealed that a mucosal strip immersed in the bath solution used for subsequent experiments did not compress when basal tension was applied. Mucosal strips were continuously agitated with a mixture of 95% O₂ and 5% CO₂ for 15–30 min to equilibrate them in the bath solution prior to drug testing. To see how the mucosal strips reacted to contraction or relaxation, the concentration of the drugs was progressively increased. A predetermined volume of stock solution was added to the tissue bath solution to achieve each concentration.

2.3. Electrical Field Stimulation Test

Electrical field stimulation (EFS) was applied using a direct-current stimulator (Grass S44, Quincy, MA, USA) connected to two wire electrodes placed parallel to the nasal mucosal strip (5 Hz, 5 ms pulse duration, at a voltage of 50 V, trains of stimulation lasting 5 s). Every stimulation session was separated by two minutes to allow for

response recovery. The nasal mucosal strip was subjected to continuous stimulation at 37 °C.

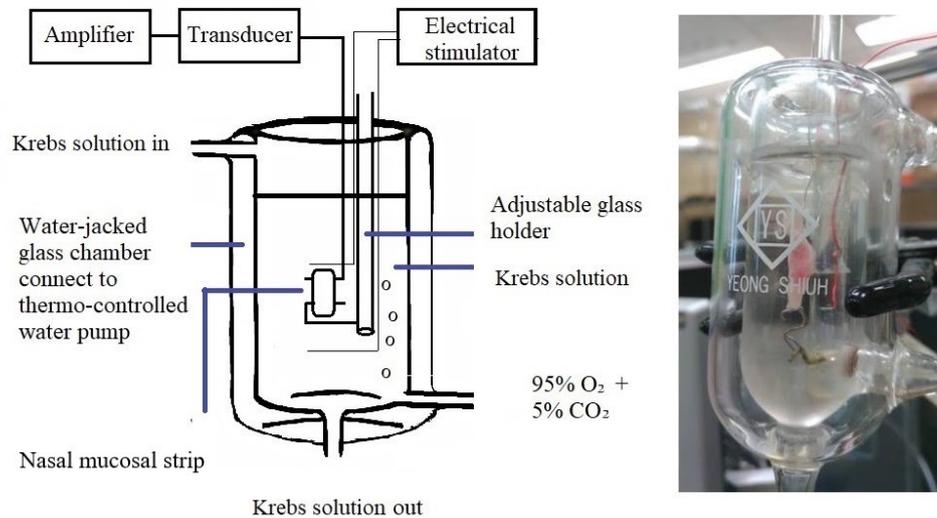


Figure 1. Schematic diagram and an actual photo of tension measurements in an isolated human nasal mucosa.

2.4. Measuring

Four methods were used to test the effects of nicotine: (1) mucosal resting tension; (2) contractions induced by 10^{-6} M methoxamine; (3) contractions induced by 10^{-6} M norepinephrine (NE); and (4) electrically produced mucosal contractions. In each experiment, a single untreated strip served as the control. The quantities detected in the 30-mL bath solution were used to calculate the drug concentrations.

2.5. Analysis of Statistics

The mean of the tension between the two introduced concentration agents was used to aggregate data from the methoxamine and baseline tension trials. The mean of the EFS peak between the two introduced concentration agents was used to collect data for the EFS experiment. A two-tailed Student's *t*-test was used to determine statistical significance; *p*-values less than 0.05 were deemed significant. The information was presented as Mean \pm SD.

2.6. Institutional Review Board Statement

The study was authorized by the Institutional Review Board of the Tri-Service General Hospital in Taipei. Every experiment was conducted in accordance with all relevant laws and regulations.

2.7. Informed Consent Statement

Informed consent was obtained from all participants involved in this study.

3. Results

The degree to which the mucosal strips were contracting or relaxing was determined by the strain applied to the transducer. Mucosal constriction caused by a small dose of methoxamine was easily noticeable and continued until the drug was removed from the tissue. When nicotine was added to the basal tension, virtually nothing changed (**Figure 2**). When added following the injection of a constricting agent, like 10^{-6} M methoxamine, it caused the nasal mucosa to relax (**Figure 3**). Higher doses of nicotine considerably relaxed the mucosal strips, while lower doses had little effect on contraction (**Figures 3 and 4**). It shows that the tension was $99.0 \pm 1.1\%$ of control values at 10^{-8} M nicotine and $26.9\% \pm 15.4\%$ at 10^{-4} M nicotine (**Figure 4**). There was a statistically significant difference in tension between 10^{-8} M and 10^{-4} M nicotine ($p < 0.05$). Higher nicotine dosages did, however, prevent spike contraction brought on by electrical field stimulation (**Figures 5 and 6**). When 10^{-8} M nicotine was added, the

peak tension of the nasal mucosal strip induced by EFS was $99.0 \pm 1.3\%$, but at 10^{-4} M nicotine, the peak was at 0 (**Figure 6**). There was a statistically significant difference in tension between 10^{-8} M and 10^{-4} M nicotine ($p < 0.01$). Adding 10^{-6} M nicotine to the 10^{-6} M NE-induced nasal mucosal contraction, it initially induced a small reduction of the contraction, then after it potentiated the contractions (**Figure 7**).

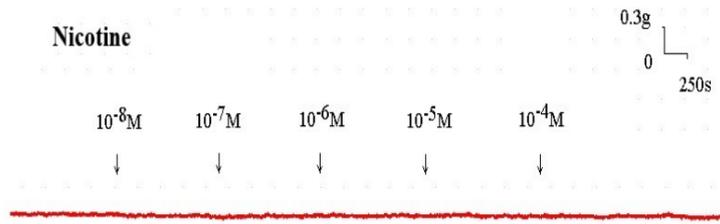


Figure 2. Tension changes in the human nasal mucosa after application of various nicotine concentrations. Nicotine alone had a negligible effect on the basal tension of human nasal mucosa as the concentration increased. The original basal tension was 0.5 g.

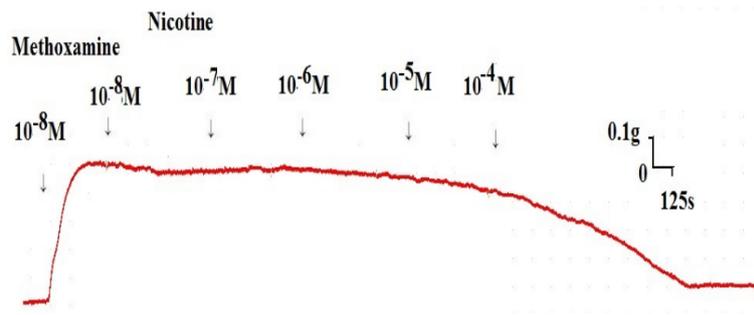


Figure 3. Original recording of the effects of nicotine on 10^{-6} M methoxamine-induced contraction of human nasal mucosa.

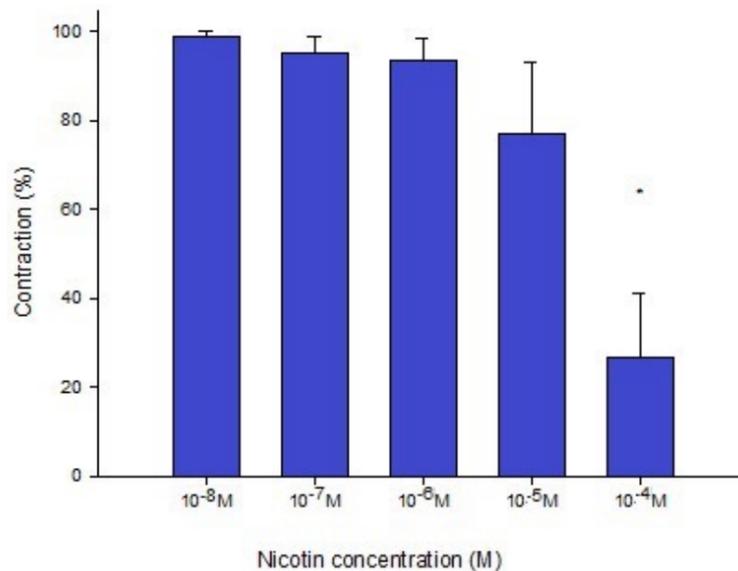


Figure 4. Effects of nicotine on 10^{-6} M methoxamine-induced contraction (contraction area calculated at 100% with no addition of nicotine) of human nasal mucosa. The difference in tension between 10^{-8} M nicotine and 10^{-4} M nicotine was statistically significant ($p < 0.05$). Results were mean \pm SD (n = 6).

Note: $p < 0.05$ compared with 10^{-8} M nicotine.

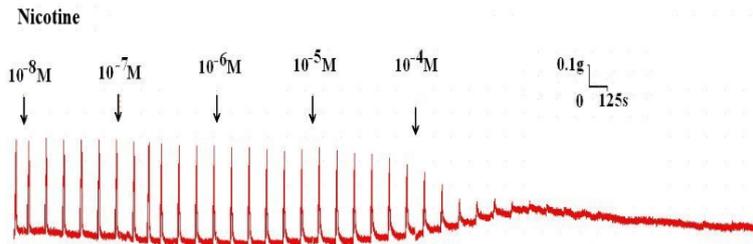


Figure 5. Original recording of the effects of nicotine on electrically induced nasal mucosal smooth muscle contractions. Higher doses of nicotine could decrease the spike contraction induced by EFS.

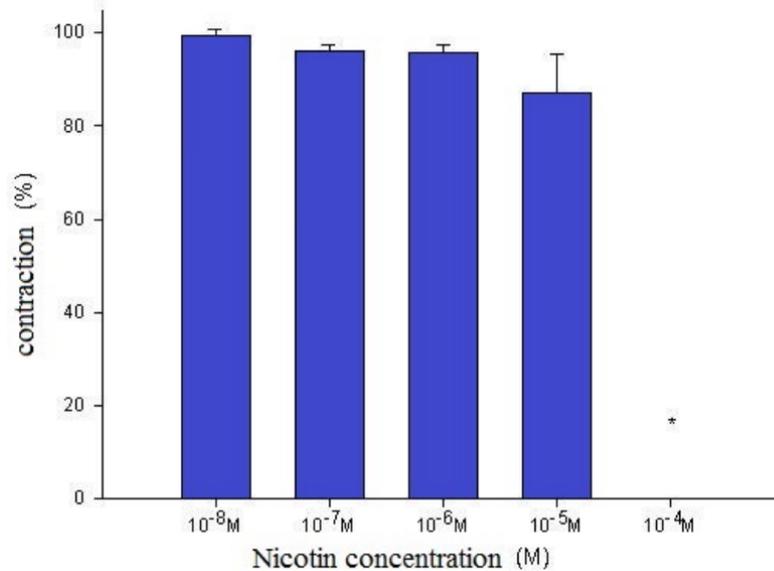


Figure 6. Effects of nicotine on electrically induced nasal mucosal smooth muscle contractions (contraction area was calculated at 100% with no addition of nicotine). The difference in tension between $10^{-8} M$ nicotine and $10^{-4} M$ nicotine was statistically significant ($p < 0.05$). Results were mean \pm SD (n = 6).

Note: $p < 0.05$ compared with $10^{-8} M$ nicotine.

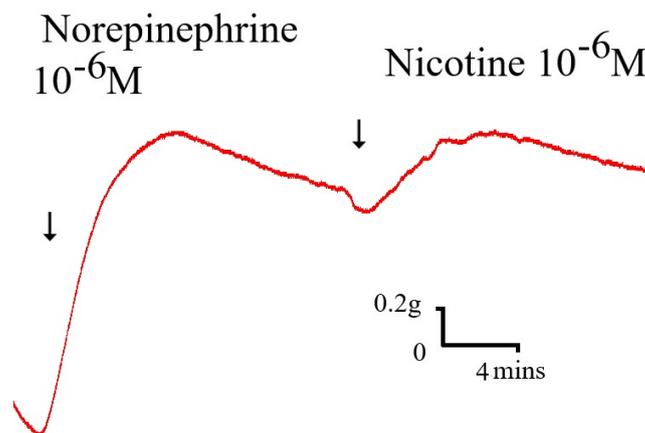


Figure 7. Original recording of the effects of nicotine on NE-induced contractions: adding $10^{-6} M$ nicotine to the $10^{-6} M$ NE-induced contractions, it initially induced a small reduction of the contractions, then after, it potentiated the contractions.

4. Discussions

The brain and muscles contain nicotinic acetylcholine receptors. Those receptors are ligand-gated ion channels. Numerous physiological and pathological activities are mediated by the α 9- and α 7-containing nicotinic acetylcholine receptors through intricate mechanisms that are currently the focus of extensive research and debate. These two types of nicotinic acetylcholine receptors may react differently in various organs or tissues [19]. Our findings are similar to those of an earlier animal study [20]. Nicotine-induced relaxation does not seem to be primarily caused by beta-adrenergic or cholinergic mechanisms [20]. The isolated nasal mucosa preparations used in our research were made from clinical surgeries, and no constricting medication (oxymetazoline or epinephrine) or local anesthetic was used, which would have made turbinectomy surgery more challenging for surgeons. Consequently, only general anesthesia was used to collect the materials from the patients. It is important to evaluate the current studies' findings in light of the test materials that were employed. To begin with, the mucosal strips were only unrefined preparations made up of veins, venules, venous sinusoids, arteries, and arterioles. Nonetheless, the smooth muscles of the vascular vessels were the only contractile tissues found in the nasal mucosa. Thus, for all intents and purposes, the contractile responses can be considered to originate from these vascular smooth muscles. In fact, it has already been established that such a preparation is capable of responding to medications and electrical stimulation [17,18]. However, the collective responses of the different tissues are probably represented by the contractile responses. Secondly, patients having a clinical diagnosis of persistent hypertrophic rhinitis provided the human nasal mucosa used in these studies. The mucosal strips were obtained from individuals with a wide range of illnesses in terms of severity and kind. Our experimental results had only negligible overall variability. Obtaining a turbinate that was "normally functioning" was impractical in order to carry out the isometric contraction testing.

As the concentrations of nicotine rose in the current investigation, the basal tension of the nasal mucosa was barely affected. These results show that nicotine cannot directly constrict vascular vessels in the nose. Previous research has shown that nicotine can raise nasal mucosal tension directly [21]. According to a prior study, a 30-min exposure to 1 mg/m³ particulate matter from secondhand smoking causes objective nasal airflow obstruction in human subjects, increases urine cotinine and tobacco-specific nitrosamines, and enhances subjective upper respiratory symptoms [22]. This discrepancy could have resulted from the post-surgery mucosal specimen's composition. As most surgeons do, they might administer an epinephrine mixture in the local anesthetic injection to reduce bleeding during a turbinectomy. According to a prior study, acute nicotine infusion may exacerbate norepinephrine-induced vasoconstriction [23]. Our study confirmed the findings. Nicotine does potentiate NE-induced contractions. There was no adrenaline present in the sample we used. And so, the previous study is compatible with our findings. Further study is needed to clarify such discrepancies.

An often-used experimental technique is electrical field stimulation, which causes the smooth muscle to contract by stimulating the nerve terminals in the tissue being studied and causing the release of endogenous neurotransmitters. It is thought that EFS causes the vascular smooth muscles to contract, causing a spike contraction of the canine nasal mucosa. However, following an ipsilateral cervical sympathetic ganglionectomy, this contraction stopped [16]. Thus, it was established that sympathetic innervations mediated the EFS-induced spike contraction of isolated nasal mucosa. As for the effects of nicotine on electrically induced nasal mucosal contractions, a high concentration of 10⁻⁴ M nicotine could block an electrically induced spike contraction; it would appear that high concentrations of nicotine did block the sympathetic effect. To determine the effects of nicotine on contraction with 10⁻⁶ M of methoxamine, the procedure examined postsynaptic events such as muscle receptor blocking, enhancement, and secondary messengers. Since a high concentration of 10⁻⁴ M nicotine reduced the contraction induced by 10⁻⁶ M of the α -adrenoceptor agonist methoxamine, it is possible that these contractions actually antagonize α -adrenoceptor functions. Many of the patients we see have nasal blockages because of quitting smoking. We also encounter a lot of heavy smokers at the outpatient department (OPD) clinics for their nasal obstruction and sleep apnea. In the past, it was challenging to find a solution to the problem of nasal patency for tobacco smokers. However, we clarify the conundrum in this work. Because nicotine can intensify the NE impact, and smoking cessation stops the potentiation, nasal blockage occurs during the smoking cessation process. However, the nasal mucosa's α -adrenoceptors appear to be damaged in long-term heavy smokers. Through antagonistic binding to α -adrenoceptors, this study showed that high nicotine concentrations had a considerable spasmolytic impact. Such phenomena caused a decrease in nasal patency in heavy smokers. However, how does nicotine antagonize the

α -adrenoceptor agonist and affect the nasal mucosal smooth muscle? The response could be significantly more complicated in an in vivo scenario than it would be in an in vitro scenario. Further studies are needed to elucidate this question.

There have been rare reports directly addressing the effect of nicotine on human nasal mucosa. In our study, a significant inhibitory effect of nicotine on human nasal vascular smooth muscle during EFS was seen, and we found a minimal effect on basal tension in vitro nasal mucosa. Finally, high concentrations of nicotine antagonized methoxamine, known as a direct-acting α -adrenergic agonist. This showed that nasal obstruction might not be relieved in patients suffering from allergic rhinitis and stuffy noses who were concomitantly using an α -adrenergic agonist nasal spray and oral or smoked nicotine.

5. Conclusion

This study demonstrated that high nicotine concentrations had a significant spasmolytic effect via antagonistically binding to α -adrenoceptors. When using an α -adrenergic agonist nasal spray plus smoking nicotine, patients with stuffy noses and nasal allergies may not see any alleviation in their nasal obstruction.

Funding

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Institutional Review Board Statement

The study was authorized by the Institutional Review Board at Taipei's Tri-Service General Hospital. Every experiment was conducted in accordance with all relevant laws and regulations.

Informed Consent Statement

Every individual participant in this study gave their informed consent.

Data Availability Statement

The corresponding author, Hsing-Won Wang, can provide the data supporting the study's conclusions upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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