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Nasal Reflexes: Reduced Sensitivity to CO_2 Irritation in Cigarette Smokers

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Abstract

Carbon dioxide inhaled through the nose in concentrations above 10% evokes nasal irritation. As concentration is increased, a non-systemic, reflexive interruption of inhalation eventually occurs in most persons. This study revealed that smokers have a considerably higher threshold for the reflex. The elevation of threshold occurred to a comparable degree in both male and female smokers, although females generally had a lower threshold than males. It therefore appears that smokers have less sensitivity to nasal irritants. This marks the first instance of a substantial chemosensory difference between smokers and nonsmokers.

Key words: cigarettes, trigeminal nerve, carbon dioxide

Introduction

Various studies have addressed possible differences in the threshold or suprathreshold chemosensory response between cigarette smokers and non-smokers.[1-9] In general, these studies have failed to corroborate the largely anecdotal report that smokers suffer chronic and substantial chemosensory deficits. The evidence is particularly weak with respect to chemosensory deficits to inhaled agents, specifically odorous stimuli.[4,8,9] Our laboratory has had interest in the physiological bases of environmental surveillance in human beings, including the role of the common chemical sense (CCS) as a protective mechanism against inhalation of hazardous chemicals.[10-12] In this preliminary communication, we report a difference in sensitivity between cigarette smokers and non-smokers toward an odorless irritant that acts via the CCS mechanism. We describe a safe, rapid, non-invasive technique to detect this difference.

Experimental

Participants

Fifty-one paid males and females with an average age of 27.3 years (SD = 7.1) participated. All gave informed consent and indicated no recent history of upper respiratory infections, asthma, emphysema or heart disease. None of the participants claimed to be on medication during the study. Cigarette smokers and non-smokers were solicited simultaneously and, before their first session, all were questioned as to whether or not they smoked regularly. Participants claiming no cigarette consumption at present and for the previous six months were categorized as non-smokers. Others indicating cigarette consumption within the last six months (smokers) were asked to report the following: (a) cumulative years of smoking; (b) current brand preference; (c) estimated consumption rate. Based upon the information provided, participants were considered habitual smokers if they met or exceeded the criterion consumption rate of one cigarette per day for five consecutive days. Two occasional smokers did not meet this criterion and were grouped together with non-smokers. AII participated in three sessions with each session given on a different day.

Apparatus

A positive-pressure gas delivery system in which the CO_2 level in a stream of compressed air could be adjusted by the investigator was used to test the participants. The system comprised a pressurized reservoir of CO_2 (Airco, Aquarator Grade), compressed air (Airco, Breathing Grade) and flowmeters (Matheson). The final flowrate (flowrate delivered to participants) was 3.5 l min^{-1}, which was held constant while CO_2 levels in the airstream were varied.

Either air alone or various concentrations of CO_2 in air were delivered to the participant *via* a single teflon tube (0.5 cm diameter; approx. 1.5 m length). This tube had a short segment of soft plastic hose fitted over the end (1.5 cm o.d. tapering to 1.0 cm o.d., 0.5 cm i.d.) to facilitate insertion into the participant's nostril. During a session, the participant held the stimulus tube and self-administered the test gas into alternate nostrils.

The participant's contralateral nostril held a thermocouple (TC) (Cu-Constantan) assembly. This consisted of TC leads threaded through the wall of a 2-cm segment of soft hose. The assembly was held in the nostril by friction. The soft plastic hose served to isolate the TC leads thermally so that air temperature alterations within the inner cylinder of the hose could be monitored continuously. The TC reference lead was placed in an ice-water bath. A single-channel output on a Grass Polygraph (Model 7) provided temperature readings in the nostril as a function of time. During actual testing, the participant's breathing pattern was recorded real-time *via* temperature changes in the nasal passageway caused by inspiration and expiration.

Procedure

Participants were seated, and instructed to insert the TC assembly, and to breathe through the nose. When given the ready signal by the investigator, the participant exhaled, inserted the end of the stimulus tube into the free nostril until snug, and then inhaled. The participant removed the stimulus tube from the nostril when the exhalation phase began. After an exhalation, the TC assembly was switched to the contralateral nostril and the test concentration was inhaled through the other nostril in an identical manner. The procedure was then repeated for the next concentration.

The participants were encouraged to breathe the stimuli as they would under normal resting conditions, i.e. without abnormally high or low tidal volumes. In order to standardize the duration of the inspiratory phase, participants had to synchronize their inhalations to an interval of two beats emitted by a metronome set at 56 beats per minute.

Carbon dioxide levels presented to the participants always increased from low (background ≈0.03% v/v) to higher values in increments of 5% CO_2, except between 0% added CO_2 and 15% added CO_2, where there were no intermediate steps. The endpoint of each session was defined as a disruption of the breathing pattern record (Fig. 1). This occurred when participants experienced a transitory interruption of inhalation during stimulation. Most sessions lasted no longer than 30 min.

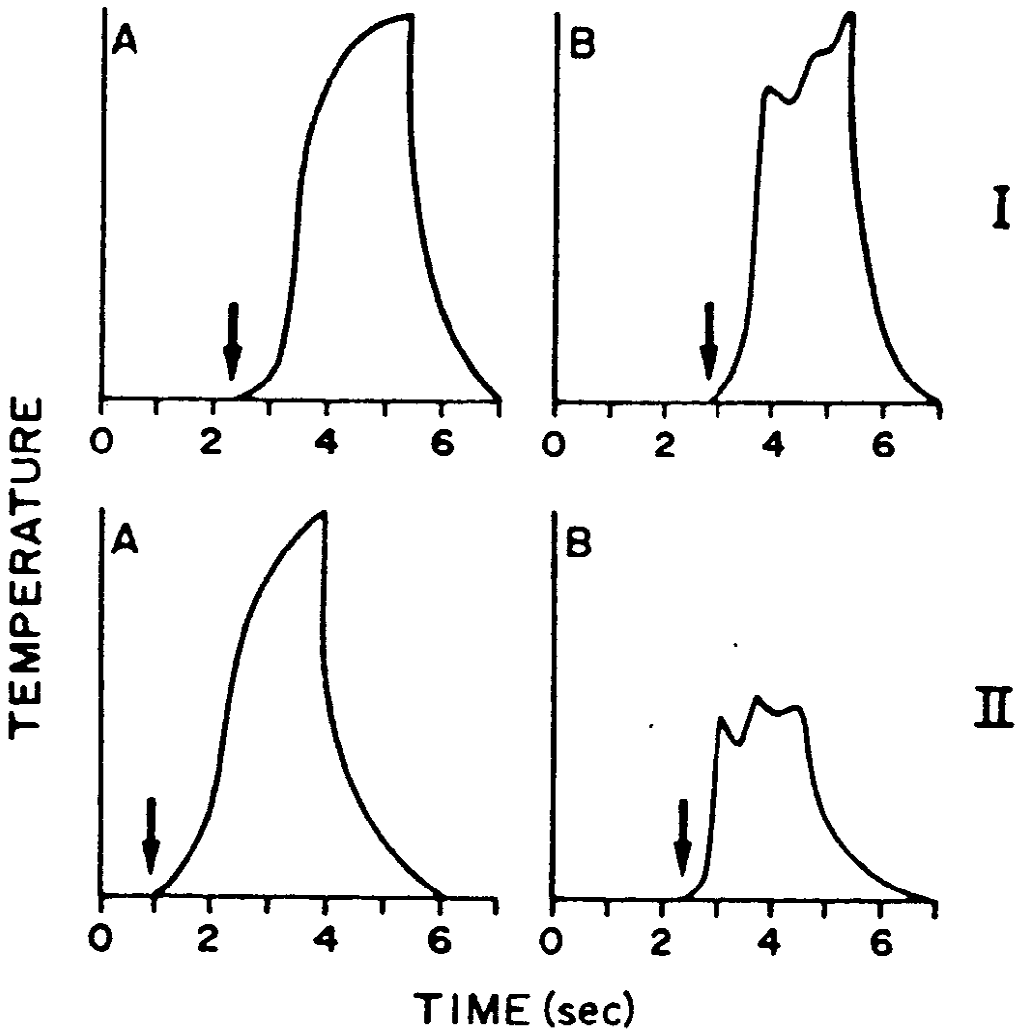

Figure 1. Examples of breathing patterns obtained with the TC placed in the nostril. With the participant breathing through the nostrils, the temperature changes correspond to inhalation (deflection away from x-axis) and exhalation (return to x-axis). The beginning of the inhalation phase is indicated by the arrow. In pairs I (smokers) and II (non-smokers), the traces labelled A were obtained under control conditions (no added CO_2 in the airstream). The traces labelled B are examples of interrupted breathing patterns obtained at threshold CO_2 concentrations in the airstream.

Results

A total of 25 smokers and 26 non-smokers were assessed for CO_2-evoked nasal reflexes. Table 1 presents the results for male and female participants in each category (smokers, non-smokers), as well as aggregate data for overall comparisons. The mean threshold CO_2 value in smokers was significantly elevated above that in non-smokers. This difference could not be explained on the basis of age because there were no significant differences in this variable

between these groups. Although a comparison of all males vs. all females showed that males have higher thresholds than females ($p = 0.05$), threshold differences between smokers or non-smokers due to gender failed to achieve statistical significance. Table 1 also shows that the magnitude of the threshold shift in smokers was higher for females than for males (≈22% CO_2 vs. ≈15% CO_2).

Table 1. Threshold CO_2 level for nasal reflex[a]

	Males	Females	Males and females combined
Smokers	84.4 ± 4.8[b] (n = 12)	78.5 ± 5.5[b] (n = 13)	81.2 ± 3.7[c] (n = 25)
Non-smokers	69.8 ± 3.9 (n = 13)	56.1 ± 7.0 (n = 13)	63.0 ± 4.1 (n = 26)
Smokers and non-smokers combined	76.8 ± 3.3[d] (n = 25)	67.3 ± 4.9[d] (n = 26)	—

[a] Values are mean CO_2 concentration (% v/v) ± SE.
[b] Differences in comparison to non-smokers of the same sex statistically significant at $p < 0.01$ (Mann–Whitney).
[c] Difference between all smokers vs. all non-smokers statistically significant at $p < 0.001$ (Mann–Whitney).
[d] Difference between all males vs. all females statistically significant at $p = 0.05$ (Mann–Whitney).

Table 2 addresses only smokers and presents a profile of cigarette use. Males in the sample smoked higher tar cigarettes than females, but other cigarette-use characteristics were comparable.

About a quarter of all smokers tested (in comparison with only one non-smoker) tolerated 100% CO_2 without exhibiting a reflex or overt signs of discomfort. This unresponsive group of smokers (n = 7; three females and four males) used high tar cigarettes: 21.2 mg and 15.0 mg tar per cigarette (average) for males and females, respectively. These persons did not differ significantly from the other smokers in age, consumption rate and cumulative years smoking. Tolerance to

high CO_2 levels was not due to an absence of the reflex mechanism in this group because higher flowrates (100% CO_2 presented at rates up to 4.8 l min^{-1}) led to the reflexes seen in other participants. Because of this unresponsive group, our results underestimated the actual difference between smokers and nonsmokers in the concentration of CO_2 necessary to elicit the reflex.

Table 2. Self-reported characteristics of smokers[a]

	N	Age	Cumulative years smoking	Tar delivery per cigarette[b] (mg)	Consumption rate (cigarettes per day)
Males	12	25.8	8.8 ± 1.6	18.6 ± 1.7	18.0 ± 3.4
Females	13	27.6	10.2 ± 2.0	11.0 ± 1.5[c]	18.9 ± 1.8

[a] Values are averages (± SE, where given).
[b] Customary brand.
[c] Significantly different from males ($p < 0.05$, *t*-test).

Discussion

The irritation evoked by CO_2 presumably results from minor pH changes brought about in the aqueous mucosal environment according to the CO_2 + H2O ⇔ H_2CO_3 ⇔ H^+ + HCO_3^- equilibria. The reflex is apparently mediated by the trigeminal nerve, which serves as the afferent pathway for common chemical sensations and acts protectively against upper respiratory tract irritation.[13,14] Peripheral stimulation of the trigeminal nerve by other chemical and physical agents is known to cause a variety of cardiovascular and respiratory reflexes in both animals and man.[10,13-18] Reflexes generated by inhaled agents characteristically occur before direct systemic action. In the case of CO_2 inhalation, nasal pungency and the accompanying reflex can occur even before the stimulus reaches the lungs. On the average, the reflex is produced 700-800 ms after inhaling a critical concentration of CO_2.

Among smokers, cigarette tar delivery was not an adequate predictor of CO_2 sensitivity. No reliable differences in CO_2 thresholds occurred between males and females, despite a difference in tar delivery of preferred brands. In an effort to discover whether or not individual differences in thresholds could be

accounted for by differences in smoking behavior, we computed correlations between threshold values and such indices as tar deliveries of preferred brands, number of years of cigarette use and consumption rate. The correlations failed to achieve significance for any parameter alone or for any simple combination of parameters. Other general parameters such as age were also insignificant.

It is not yet clear why smokers should be less sensitive to stimulation of the nasal mucosa. The typical smoker does not circulate much smoke through the nose and the sense of smell seems unimpaired or, at most, trivially impaired by smoking.[4,8,9] Because cigarette smoke contains ciliostatic agents,[19,20] there may be important qualitative and quantitative differences between smoker and nonsmoker in the mucus layer overlying the free nerve endings of the trigeminal nerve.[21] Perhaps the nasal mucosa is particularly vulnerable to such agents. On the other hand, because a range of CO_2 thresholds was also seen in non-smokers, it is possible that cigarettes tend to be used by individuals with inherently low CCS sensitivity. It would be of interest to test this by determining whether or not changes in reflex thresholds occur in people who give up smoking.

The CCS has an important role in protecting the body against inhalation of irritating substances. Our data are consistent with the idea that, in comparison to a similar population of non-smokers, male and female smokers experience less sensory effect from odorless irritants in air. Insensitivity to irritants may lead to higher exposures to hazardous chemical agents in occupational settings.

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