Tobacco cigarette smoking and patellar reflex depression

One hundred fifteen young men served as subjects to determine the effects of smoking cigarettes of differing nicotine content on the patellar reflex. Each volunteer smoked 2 of the same kind of cigarettes in a 4 minute period with an interval of 25 minutes between. The patellar reflex was elicited automatically every 2 seconds by a reflex hammer attached to a solenoid. The reflex was recorded with the use of a strain gauge transducer and the electromyogram of the ipsilateral quadriceps femoris muscle. A negligible depression was produced by smoking a nicotine-free lettuce cigarette. A low-nicotine tobacco cigarette showed approximately 45 per cent depression within 5 minutes compared with a 67 per cent depression after smoking a high-nicotine cigarette. The depression caused by the second cigarette was comparable in degree and duration to the effect of the first cigarette. No accumulative or tachyphylactic effect was observed. It is concluded that tobacco smoking produces a remarkable, short-term depression of the human skeletal-motor system. The depression of the patellar reflex seems to be related to the nicotine content of the cigarette smoked.

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The report of the Advisory Committee to the Surgeon General of the United States Public Health Service on "Smoking and Health" summarizes evidence on this controversial subject.[15] There is no general agreement as to why some people continue to smoke. Surely it must be because of various complex pharmacological and psychological reinforcements. As neuropsychopharmacologists, our own bias prompts us to seek various pharmacological reinforcements of tobacco smoking, especially those related to the central nervous system. For some time we have been concerned with delineating the central actions of nicotine and tobacco smoking in animals.[4-6, 11] These studies have convinced us that some of the most important actions of small amounts of nicotine as present in tobacco smoke are on the central nervous system.

Although much is known about the actions of nicotine on the central nervous system of animals, relatively little is known about the central effects of tobacco smok-

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ing in human beings. Marked cardiovascular and gastrointestinal effects have been reported.[1] The effects of nicotine and smoking on the human central nervous system are much less defined.[14] Inasmuch as nicotine produces a dramatic reduction of the patellar reflex of animals, probably as a result of a direct action of the central nervous system,[8] it would be of considerable interest to know if this pharmacological effect can be produced in man by small doses of nicotine as absorbed during cigarette smoking. Clark and Rand[2] have shown that the human patellar reflex is depressed by cigarette smoking. In their study, cigarette smoking had a much more pronounced effect in nonsmokers and light smokers than in heavy smokers. Smoking cigarettes containing an amount of nicotine comparable to commercial cigarettes (2.1 per cent) inhibited the patellar reflex in a significantly greater number of subjects than did smoking cigarettes with a low nicotine content (0.1 per cent). An independent unpublished observation, by one of us some time ago, that tobacco smoking had a profound effect in reducing electromyogram artifact during electrical recordings of brain wave activity in anxious patients, prompted us to undertake a systematic study of the effects of tobacco smoking on skeletal muscle tone. It has been reported[19] that cigarette smoking causes a dramatic but transient reduction in skeletal muscle tone in spastic patients. In view of the fact that the human patellar reflex is easily elicited and measured, it seemed an ideal end point for determining at least one major effect of tobacco smoking. This article reports some of the results obtained with normal volunteers who smoked cigarettes of varying nicotine content.

Methods

Subjects. The experiments were performed on 115 healthy men between 17 and 29 years of age. All of them were asked not to smoke for 12 hours before the experiment. Those who did not comply were excluded from testing. The subjects were classified as nonsmokers, light smokers (1-3 cigarettes a day), moderate smokers (3-20 cigarettes a day), and heavy smokers (more than 20 cigarettes a day). In 17 cases the same subject was investigated on 3 different days in which a cigarette of different nicotine content was used in a random fashion. The rest of the subjects were tested with only one type of cigarette. Prior to the study a complete medical examination was given to exclude subjects with physical or mental abnormalities. Four subjects were rejected because of hyporeflexia. Subjects taking drugs within 2 weeks of the experimental sessions were also excluded. The experiments were carried out in the morning. Most of the subjects had breakfast several hours before the experiment.

Experimental procedure. The experiment consisted in smoking 2 cigarettes with an interval of 25 minutes between. The patellar reflex was elicited with a mechanical rubber-tipped hammer and monitored before, during, and after smoking by recording simultaneously the isometric contraction with a Grass Model FT 10 strain gauge and the electromyogram of the quadriceps muscle by surface electrodes attached to the overlying skin. An Offner polygraph was used for recording.

Three different cigarettes with varying nicotine content were used. These were lettuce cigarettes which contain no nicotine and tobacco cigarettes with a nicotine content of 0.80 and 1.69 mg. per cigarette.[13] In the beginning of the experimental series before nicotine-free cigarettes were available, sham smoking was performed by taking puffs from an unlighted cigarette or by inhaling air through a cotton-filled glass tube. A typical experiment consisted of a control period of 10 minutes during which the subject relaxed in horizontal position with the use of pillows to make him as comfortable as possible. Smoking was started after 10 minutes or later, when steady patellar reflex responses were obtained. The subject was advised to smoke each cigarette in a series of deep inhaling

puffs within a period of 4 minutes. Each cigarette was smoked to approximately 2.5 cm. butt length. The second cigarette was smoked 25 minutes after the first.

The patellar reflex was elicited mechanically every 2 seconds. The hammer exerted a pressure of about 0.5 Kg. upon hitting the patellar tendon. The knee joint was flexed to about 90 degrees during the resting state. The distal part of the lower leg was connected by a chain to the strain gauge. The surface electromyogram was recorded bipolarly with Grass electroencephalogram electrodes. One electrode was placed above the quadriceps muscle in the middle of the upper leg, the other one was placed 1 cm. proximal to the patella. The ground electrode was placed in the middle. An A.C. differential amplifier with a time constant of 0.1 msec. and 100 microvolts per centimeter amplitude was used.

Evaluation of data. Since the amplitude of the patellar reflex showed marked individual variation, all data were transformed as percentage of control. Only experiments in which a steady state of reflex responding was maintained for at least 5 minutes before tobacco smoking were included in these studies.

Results

General observations. At the beginning of the experiment, marked variability of the patellar reflex was observed. With time, as the subject relaxed, a more constant reflex amplitude was obtained. Frequently, slight habituation or accommodation of reflex activity was observed. Several subjects showed an actual increment during the first 10 minutes of recording. The experiments with sham smoking and with nicotine-free cigarettes revealed that when a steady state was reached within the first 15 minutes no further habituation or accommoda-

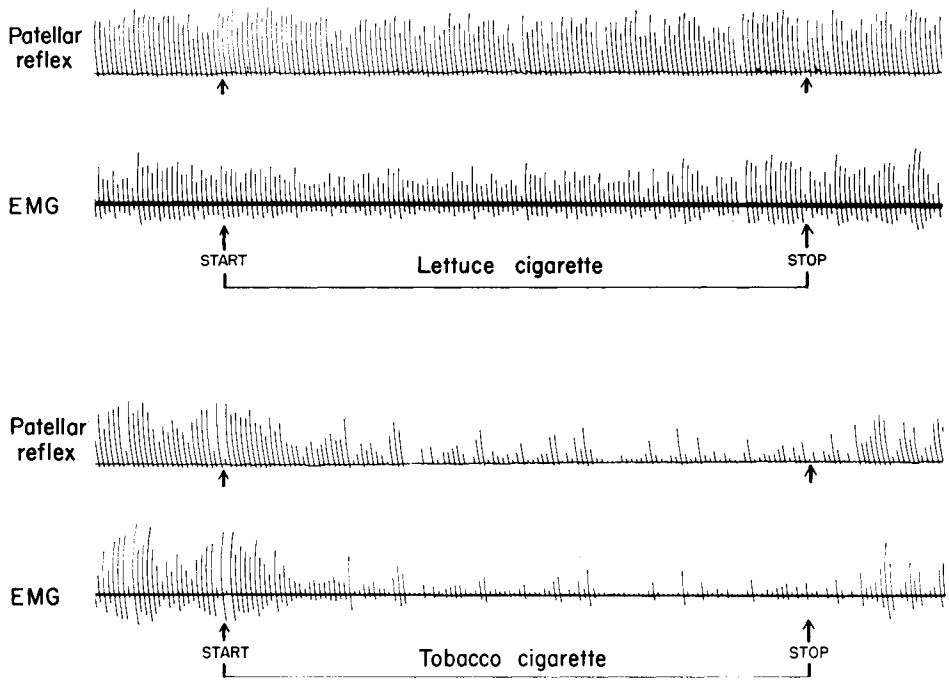

Fig. 1. Portions of a typical polygraph tracing of the isometric recording of the patellar reflex and the EMG response of the quadriceps femoris muscle to smoking a tobacco and lettuce cigarette. Note the marked correspondence of the amplitude of muscle tension and EMG. The time base represents the tapping of a patellar tendon automatically every 2 seconds. During the 4 minute period the 2 cigarettes were smoked to approximately the same butt length of 2.5 cm.

tion appeared during the following 60 minutes of reflex recording.

The amplitude of the electromyogram of the quadriceps femoris was highly correlated with the amplitude of the mechanical response. Alteration of the respiratory pattern when smoking started led to slight changes in reflex activity. In most cases, an early slight facilitation of the patellar reflex was observed beginning almost immediately after smoking. This facilitation appeared irrespective of sham smoking, smoking nicotine-free cigarettes or smoking nicotine-containing cigarettes. However, the facilitation was quite variable. Some individuals showed an early slight depression instead. The mean of 20 cases showed an increase of about 11 per cent reflex activity during the first 15 seconds after beginning smoking.

Subjects who smoked nicotine-containing cigarettes invariably obtained a marked depression of the patellar reflex as recorded mechanically, as well as in the electromyographic response as illustrated in Fig. 1. A portion of the actual record from a typical subject is shown to illustrate the response to 2 types of cigarettes. Following a nicotine-containing cigarette, depression of the patellar reflex was observed about 30 sec-

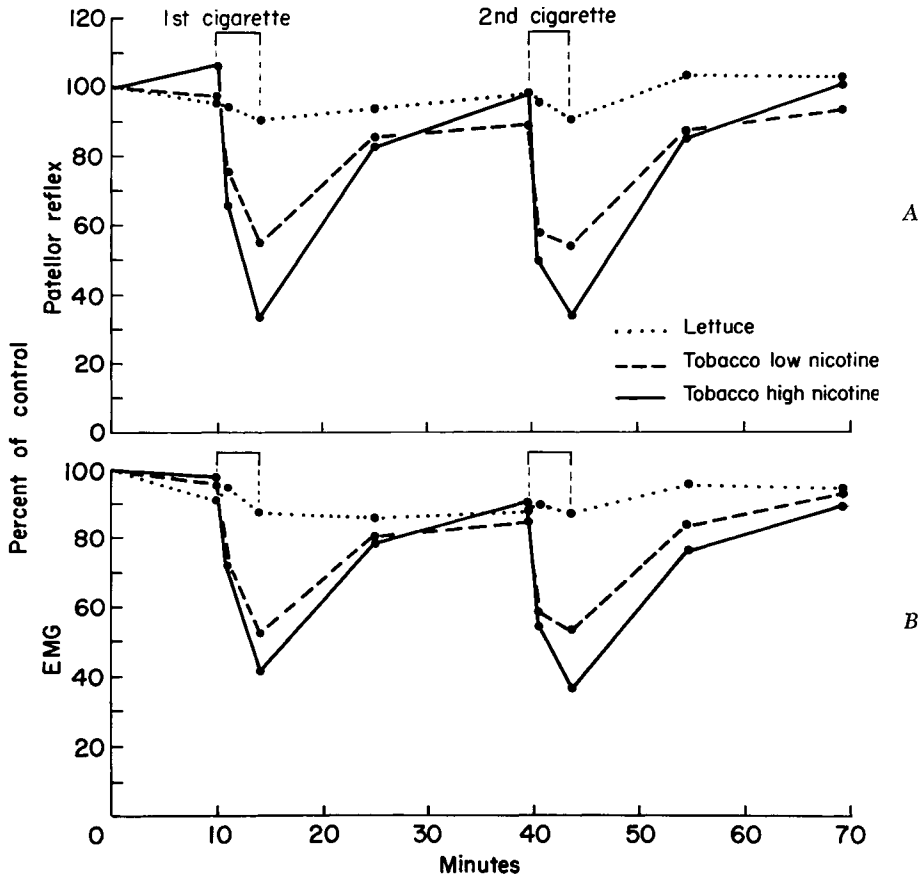

Fig. 2. Effects of smoking cigarettes of differing nicotine content on the mean patellar reflex and EMG. *A*, Mean patellar reflex. The dotted line represents the mean amplitude of 22 subjects smoking lettuce cigarettes. The dashed line represents the mean amplitude of 19 subjects smoking low nicotine-containing cigarettes. The solid line represents the mean amplitude of 16 subjects smoking high nicotine-containing cigarettes. *B*, Electromyogram of the quadriceps femoris muscle. The data on the same subjects are plotted as above.

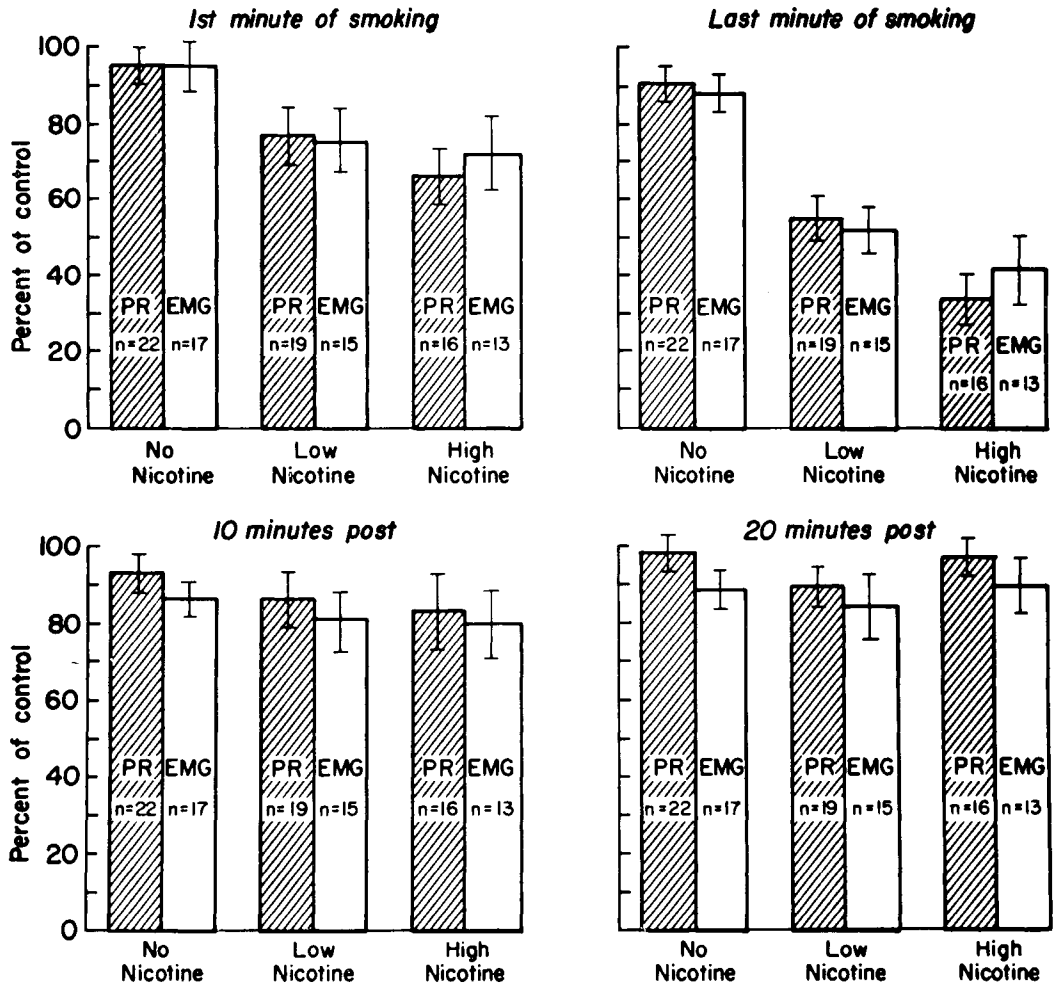

Fig. 3. Bar graph of the effects of smoking cigarettes of differing nicotine content on the mean amplitude of the patellar reflex and EMG. The means ± the standard error (SE) are given at various times before and after smoking cigarettes of varying nicotine content. The nicotine content is listed below each type of cigarette smoked. All data are represented as the per cent change of the control period.

Table I. *Per cent change in the mean amplitude of the patellar reflex and the EMG of the*

Type of cigarette	*Parameter*	*Number of subjects*	*First minute after smoking*	
			Mean ± S.E.	*P value**
Lettuce (no nicotine)	PR	22	95.0 ± 4.6	—
	EMG	17	94.7 ± 6.3	—
Tobacco (.80 mg. nicotine)	PR	19	76.5 ± 7.3	$< .05$
	EMG	15	75.1 ± 8.6	$< .1$
Tobacco (1.69 mg. nicotine)	PR	16	66.1 ± 7.6	$< .01$
	EMG	13	72.1 ± 9.8	$< .05$

*Compared to lettuce cigarette, group comparison student t test.

onds after the initial facilitation (if there was any). The depression of the patellar reflex was progressive and reached its peak at the end of smoking. The depression was always steeper during the first minute than during the last 3 minutes of smoking.

After smoking, the depression remained at the same level or increased slightly for a period of 30 to 120 seconds. Following this period of depression, progressive recovery was observed. The curve of recovery was steeper within the first 10 minutes than later. Twenty-five minutes after the end of smoking, the reflex response in all but one case returned toward control levels.

When full recovery was obtained the subject was asked to smoke a second cigarette of the same nicotine content. The induced depression of the patellar reflex quickly reappeared and resembled closely the depression following the first cigarette. The mean data of all subjects is illustrated in Figs. 2 and 3 and Table I.

Marked mean differences in the depression of the patellar reflex were found according to the nicotine content of the cigarettes smoked. Nicotine-free cigarettes caused no more depression than that of normal habituation of the reflex during sham smoking. Cigarettes with a nicotine content of 0.80 mg. produced about 45 per cent depression of the patellar reflex. Cigarettes with a nicotine content of 1.69 mg. produced 67 per cent depression of normal.

In view of the fact that heavy smokers show tolerance to nicotine, it was of interest to determine the differential effects of smoking high nicotine-containing cigarettes on non- and heavy smokers. Fifteen nonsmokers were chosen on the basis that they could inhale. Most of them had smoked but stopped for at least 6 months to as long as 3 years previously. Seven smokers were chosen on the basis they smoked one pack or more of cigarettes per day and were able to stop smoking 12 hours prior to the experiment. The mean depression of the patellar reflex ± SE for each group of subjects was determined. Occasionally nonsmokers were observed who showed a greater depression of their patellar reflex after the first cigarette, but this was not a constant finding for all of them. The heavy smokers, deprived of cigarettes for 12 hours, tended to show a greater depression of their patellar reflex than the nonsmokers. The reason for this was not apparent but might be related to the fact they inhaled much better. Further studies are now in progress to elucidate this phenomenon. There was no evidence that these deprived heavy smokers were more resistant to high nicotine-containing cigarettes.

Side effects. Twenty-nine of the 115 subjects complained about slight to moderate dizziness during smoking. Most of these were nonsmokers, but even some of the habitual smokers felt uneasy because the deep smoke inhalations in a relatively short period of time were somewhat unusual.

adriceps femoris muscle at various times during and after cigarette smoking

4 minutes after smoking		*10 minutes after smoking*		*20 minutes after smoking*	
Mean ± S.E.	*P value**	*Mean ± S.E.*	*P value**	*Mean ± S.E.*	*P value**
90.8 ± 4.0	—	93.2 ± 5.0	—	98.4 ± 4.8	—
87.9 ± 4.9	—	86.5 ± 4.8	—	88.4 ± 4.9	—
55.3 ± 5.8	< .001	86.4 ± 7.1	< .5	89.6 ± 5.0	< .9
52.0 ± 6.2	< .001	80.6 ± 7.8	< .6	84.2 ± 8.4	< .7
33.8 ± 6.7	< .001	83.3 ± 9.8	< .4	97.1 ± 5.1	< .9
41.6 ± 8.8	< .001	79.7 ± 8.7	< .5	89.7 ± 7.2	< .9

Paradoxically, subjects who did not have breakfast before the experiment complained more often about these side effects than those with breakfast. Some of the nonsmokers failed to inhale correctly. The data from these cases had to be excluded from evaluation.

Discussion

The results of this study clearly indicate that the human patellar reflex is depressed following smoking of tobacco-containing cigarettes. Furthermore, the extent of the induced depression depends largely on the nicotine content of the cigarette. The depression of the patellar reflex was fully reversible and of short duration.

Smoking a second cigarette 25 minutes after the first resulted in a reproducible homologous depression indicating that no accumulation nor tachyphylaxis took place at this interval of time. Contrary to the study of Clark and Rand,[2] no significant differences were found between smokers and nonsmokers. The latter fact might be due to the long period (at least 12 hours) that each subject abstained from smoking and from the fact that we never really had subjects who smoked as heavily as those studied by Clark and Rand.

In our experiments with sham smoking and nicotine-free cigarettes, no significant depression was noted in the majority of subjects. Inasmuch as smoking produces a very large number of miscellaneous chemicals including CO, CO_2, etc., the observed depression of the patellar reflex could be due to a large variety of substances other than nicotine. Carbon dioxide, in particular, is known to depress the patellar reflex in concentrations easily obtainable upon inhaling smoke.[9, 10] However, the fact that smoking nicotine-free cigarettes, which also cause the release of many products of combustion and pyrolysis, did not produce reflex depression makes unlikely an effect of such miscellaneous compounds. The fact that the high nicotine-containing cigarettes were also more effective further supports the conclusion that the depression of the patellar reflex is due to inhaled nicotine. That nicotine is critically involved in the tobacco-smoking habit has recently been shown by Lucchesi and associates.[12]

No conclusion can be drawn concerning the site of action of the resulting patellar-reflex depression. Nicotine is known to act on many different levels of the motor system. For example, from the classical studies of Henatsch, Eldred, Fujimori, Smith, and their co-workers (see review by Smith[16]), it is known that nicotine is one of the most potent stimulants of muscle spindle afferents, both extensors and flexors. This could result in inhibition of the patellar reflex. Furthermore, inasmuch as nicotine is a powerful stimulant of Renshaw cells in the spinal cord, it could be acting centrally.[3, 7] This problem has been discussed by Ginzel.[8] He has offered evidence (on the basis that, in the cat, mecamylamine blocked nicotine-induced depression of the patellar reflex, but hexamethonium did not) that the major effect of nicotine was central. This agrees with our earlier studies[17] that intravenous doses of nicotine in the order of 20 μg per kilogram (doses comparable to those absorbed by tobacco smoking in man) were very effective in stimulating Renshaw cells. However, studies similar to those of Ginzel in cats, as well as in patients with spinal transections, need to be performed to demonstrate the site of nicotine-induced depression of the human patellar reflex.

The clear-cut and highly significant depression of the patellar reflex by smoking nicotine-containing cigarettes encourages further studies in which this predictable end point is used as a measure of the pharmacological effect of smoking. The cigarette-smoking experiments could be extended to patients with varying levels of anxiety and motor hyperactivity. It may very well be that some of the reduction of skeletal muscle tension thought to occur during tobacco smoking may be on this basis.

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