Cigarette smoking, blood lipids, and baroreceptor-modulated nociception*

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Abstract. Activation of arterial blood pressure has been shown to influence higher central nervous activity. In animals, induction of sleep-like states and increases of seizure and pain thresholds in response to baroreceptor stimulation have been reported. In certain human groups, mechanical stimulation of the carotid baroreceptors also increases pain thresholds. The present paper examines the hypothesis that smokers show baroreceptor dependent antinociception as compared to non-smokers. It is speculated that one effect which rewards smoking is the nicotine induced phasic blood pressure increase which leads to baroreceptor stimulation and dampens pain perception. One hundred and twenty subjects were investigated using a recently developed mechanical baroreceptor stimulation technique and an electrical pain stimulus. The group of heavy smokers showed the predicted effect: their pain thresholds were enhanced during conditions of increased baroreceptor activity as compared to the control condition. The group of medium, light and non-smokers, however, did not show this effect. Neither blood lipid levels nor diastolic or systolic blood pressure paralleled the group differences on baroreceptor dependent antinociception. In heavy smokers, the nicotine induced phasic blood pressure increases might have baroreceptor dependent pain dampening effects, which might be among the reinforcing qualities of smoking.

Key words: Pain – Baroreceptor stimulation – PRES – Smoking – Nicotine – Blood lipid levels – Cholesterol

There is accumulating evidence that baroreceptor activation has effects on cortical arousal: Koch (1932) was the first who observed that mechanical stimulation of the arterial baroreceptors evoked sleep-like states in dogs. Gellhorn, Yesinick, Kessler and Hailman (1942) reported that seizure thresholds were increased due to mechanical

or pharmacological stimulation of the baroreceptors. Bonvallet, Dell and Hiebel (1953) observed EEG synchronization during stimulation of the baroreceptors. Elbert and coworkers (1988) and Rau et al. (1988) reported decreases in the negativity of slow cortical potentials of the EEG in humans after mechanical baroreceptor stimulation using the neck cuff technique developed by Eckberg, Cavanaugh, Mark and Abboud (1975). Rau, Elbert and Birbaumer (1992) found antinociceptive effects of a controlled mechanical baroreceptor stimulation technique in humans. Dworkin et al. (1979) studied rats with intact and surgically destroyed baroreceptors under conditions of pharmacologically enhanced blood pressure and found that blood pressure increased pain thresholds in rats only if baroreceptors were left intact. Studies on humans uniformly showed that there are large inter-individual differences of the antinociceptive effects of baroreceptor activation on nociception: in the study of Elbert et al. (1988), only subjects with elevated tonic resting blood pressure showed antinociception, but not subjects with normal blood pressure levels. Rau (1989) found that the degree of risk for the development of hypertension as measured by a bicycle ergometer test (Franz 1986) was positively and significantly related to the degree of antinociception due to baroreceptor stimulation.

Nicotine is known to phasically increase cardiovascular activity (Benowitz et al. 1990) and hence stimulate baroreceptors. Depending on the dose and situation, nicotine has arousing and dampening effects on the central nervous system. Ashton and colleagues (1980) studied the contingent negative variation (CNV) of the EEG as a measure of cortical arousal and found that low doses of nicotine enhanced the amplitude of the CNV, whereas high doses of nicotine decreased the CNV amplitude, indicating cortical inhibition in response to high doses of nicotine. However, there was (Ashton et al. 1974) considerable variation between subjects in the threshold for the switch from CNV stimulation to CNV inhibition. As a result, the relationships between nicotine effects on the cardiovascular system and on the CNV are unclear, particularly with respect to critical dosage thresholds. By measuring the frequencies of the spontaneous EEG wave

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forms, Mangan and Golding (1978) found that nicotine has dampening effects on cortical arousal if applied during conditions of high arousal (white noise exposure) as opposed to low arousal conditions in which nicotine had stimulating effects on cortical activity.

It might be of interest to propose a link between the cardiovascular stimulatory and cortical inhibitory effects of high dosage nicotine. Is phasic blood pressure increase, caused by smoking and followed by baroreceptor activation and cortical inhibition (at high doses), one mechanism which rewards smoking? As not all people show the cortical inhibition due to baroreceptor stimulation (Zamir and Shuber 1980; Larbig et al. 1985; Elbert et al. 1988), heavy smoking should be highly effective in those subjects who show the baroreceptor dependent brain effects. Consequently, if this hypothesis is true, we should find a stronger baroreceptor induced pain dampening in subjects who smoke heavily compared to subjects who do not smoke, or who smoke in moderation.

Data on risk factors for cardiovascular diseases, consisting of blood lipid data (total cholesterol, HDL, LDL, LDL/HDL) and a 1 week daily home recording of blood pressure, smoking behavior, athletic activity, alcohol and coffee consumption, stress, and pain was collected. This data was collected both to check for any differences on the non-smoking factors between the different smoking levels investigated in the current sample and as part of a separate longitudinal study.

Materials and methods

Subjects. One hundred and twenty healthy volunteers (80 men and 40 women) aged 22 – 53 years (mean 31.4 ± 6) participated in this study. All subjects were employed by local companies and received a payment of 100 DM for their participation. Prior to participating in the study, all subjects were required to complete a health status questionnaire and sign a consent form that summarized the experimental protocol. Exclusion criteria were cardiovascular, neurological or psychiatric disorders. The study's protocol was approved by the Ethical Committee of the Faculty of Clinical Medicine of the University of Tübingen.

Baroreceptor stimulation. Baroreceptor stimulation was conducted according to the PRES (phase-related external suction) method described in detail by Rau et al. (1992). A malleable neck cuff, fashioned from lead plate and coated to prevent contact with the skin, was designed according to the description given by Eckberg et al. (1975). A foam rubber sheet was attached to the edge surfaces of the cuff to insure subjects comfort and to maximize the air-tightness of the cuff. The cuff was positioned on the subjects neck and secured with an elastic band. The PRES neck-suction technique was implemented by a specially designed device, the basis of which is an electrical motor which produces an air current in a closed chamber (20 cm width, 30 cm long, 15 cm high; Fig. 3 in Rau et al. 1992). This current of air is directed to the neck cuff by opening and closing four different valves, which regulate air flow into and out of the chamber. The electromagnetic couplers were controlled by the computer, so that the changes in air flow to the cuff could be synchronized to the heart cycle. Changes in local cuff pressure from -30 mm Hg to $+10$ mm Hg could be achieved within 180 ms of the valve operation.

Baroreceptors are stretch receptors sensitive to changes in transmural pressure, which are normally induced by transient increments and decrements in intravessel pressure (Mancia 1983). The baroreceptors can also be stimulated by changes in extravessel pressure

(e.g., neck cuff pressure), as well as by a combination of extra- and intravessel pressures. The traditional neck cuff technique varies the extravessel (cuff) pressure for intervals of some seconds. During stimulatory trials, a negative pressure is applied to the neck and during inhibitory trials, positive pressure is applied to the neck. As negative and positive cuff pressure could be easily discriminated by the subjects, and most subjects report different degrees of discomfort to both conditions with more discomfort during the stimulation trials, the traditional baroreceptor neck suction technique does not allow the application of a control condition which controls for this differential perception of the two trial types. Different responses to the different conditions could be a consequence of both different baroreceptor activation as well as different psychological conditions like distraction or discomfort during one condition. PRES, on the other hand, allows the application of a stimulation as well as a control condition which are not perceived as different. (Furedy et al. 1992). PRES uses the principle that “*application of a brief external suction burst during systole enhances the pulse amplitude by addition with the intravascular pressure peak; whereas exactly the same brief external burst applied later, in diastole, reduces the pulse amplitude.*” (Dworkin 1988, pp 46–47). During the stimulation condition, a pulse of negative pressure (suction) coincided with the systole and the passing of the pulse wave at the carotid, whereas a positive pressure pulse (blowing) was given during the diastole. In the control condition, a positive pressure pulse was delivered during the systole and negative pressure was produced in the neck cuff during the diastole. In both conditions, positive (or negative) pressure pulses commenced 100 ms following detection of the interbeat interval as recorded during the previous trials minus 100 ms. The pressure pulse produced during diastole directly followed that given during systole, both having the same duration. This sequence was repeated for a duration of 6 s for each trial, resulting in a train of positive, negative and neutral cuff pressures.

Electrical pain stimuli and psychometric procedures. Subjective magnitude estimations of suprathreshold stimuli were determined during both trials in which baroreceptors were stimulated and control trials. The electrical stimuli were generated by a specially designed optically isolated, constant current, stimulus generator. This device produced bipolar electrical impulses. The entire stimulus duration was 10 ms. These electrical impulses were applied via an intracutaneous electrode to the tip of the left middle finger (as described by Bromm 1985; and Miltner et al. 1988). To reduce cutaneous resistance and lower sensory thresholds, the epidermis was removed with a hand-held dental burr (diameter 1 mm). Subjective magnitude estimates were determined for stimuli presented either during pressure pulses delivered during systole or diastole, with a 100 ms delay following the change in cuff pressure. After every trial, subjects rated the pain sensitivity on a visual scale presented on a computer screen. By pressing a button, subjects could move a target on the computer screen to the position which indicated the perceived pain. The scale ranged from “no perception” (0) to “strong pain” (25). Each subject's pain threshold was determined before the experiment began. The stimulus intensity which was determined as being painful was used unchanged during the whole experiment.

Physiological recordings. The electrocardiogram was measured through Beckman Ag/AgCl electrodes attached to the right clavicle and lower left rib cage. Electrode sites were cleansed with alcohol and rubbed with an abrasive jelly to improve contact. The R-wave of the electrocardiogram was detected by a Beckman cardiometer and fed to an IBM-AT compatible computer that measured the interval between successive R-waves to within ± 0.5 ms. Inter-beat intervals were computed off-line.

Procedure. The experiment reported in this paper was part of an experimental session of the initial step of a longitudinal study involving 120 healthy subjects. The aim of this longitudinal study is to determine contributions of psychophysiological mechanisms including baroreceptor effects on the brain and behavior for possible development of hypertension. The first step of this study included

one laboratory session which lasted about 4 h. During this session, a bicycle ergometer test with a 3 min work load period, two resting periods and two mental arithmetic periods were presented to each subject. Smokers were asked to smoke one of their own cigarettes after completion of the first rest and mental arithmetic periods and before presentation of the second resting and mental arithmetic periods. Non-smokers had a break of 10 min at this time. For that reason, the smokers were not in a deprived state. At the end of the session, the baroreceptor manipulation and pain evaluation experiment was performed. Finally, venous blood (10 ml) was taken in order to determine blood lipid levels. The order of experiments was identical for all subjects. Data from the longitudinal studies will not be reported in this paper.

The baroreceptor experiment included 64 trials. One half of the trials were baroreceptor stimulation trials, and the remaining 32 trials were control trials. The sequence of trials was pseudo-randomized. Each trial consisted of a 1 s baseline period, a 6 s baroreceptor manipulation interval during which the cuff was activated, and a 1 s post baseline period. During each trial, an electrical pain stimulus was delivered to the right index finger in order to evaluate effects of baroreceptor stimulation on pain perception. This happened after the first or fourth heart beat within the baroreceptor manipulation interval. After each trial, subjects rated the pain intensity on a visual analog scale presented by a computer screen. The inter trial interval was varied pseudo-randomly between 12 and 19 s. Subjects sat in a comfortable position in a reclining chair. They were instructed to stay alert and relaxed during the trials. Timing of trials, creating of the pseudo-randomized order of conditions, presentation of pain stimuli, and storing of ratings and R-waves of the EKG was performed by an IBM compatible computer which was programmed using the ASYST language.

Statistical analyses. Subjects were divided into four groups on the basis of the daily records of cigarette smoking compiled by every subject for 1 week. The group of nonsmokers consisted of 34 subjects. Twenty subjects reported daily cigarette consumption between 1 and 11 cigarettes and were classified as light smokers. Thirty-one subjects who smoked between 12 and 20 cigarettes daily were classified as medium smokers. Eighteen subjects smoked more than 21 cigarettes per day [averaging 25 (4.8)] and were classified as heavy smokers. The remaining 17 subjects did not complete the diaries and were excluded from further analyses. In a previous study (Pickert et al. 1992) we found that self reported cigarette consumption was correlated highly with urinary cotinine level. In order to evaluate whether the smoker groups differed on important data regarding the cardiovascular system, data from the daily records (systolic and diastolic blood pressure, heart rate, athletic activity,

coffee consumption, tobacco consumption) and the blood lipid data (total cholesterol, HDL, LDL, LDL/HDL) were subjected to one-way ANOVAs containing the factor Group (non-smoker or light, medium and heavy smokers). Significant group effects were followed up with Scheffe' post hoc tests. Data from the baroreceptor experiment (heart period responses and subjective magnitude estimates) were subjected to a mixed model ANOVA containing the four-level Group factor and the repeated measures factor Condition (baroreceptor stimulation versus control condition). Alpha was set to 0.05.

Results

General data

Table 1 contains results for general data including blood lipid values. Neither systolic nor diastolic *blood pressure* differed between groups. *Heart rate* reached significance [$F(3,103) = 7.3$; $P < 0.001$] due to the fact that heart rate was significantly lower in the non smoking group as compared to both the medium and heavy smokers. There was no significant group difference for the overall duration of *weekly athletic activity*. *Coffee consumption* showed a significant group difference [$F(3,101) = 3.59$; $P < 0.02$], and post-hoc examination revealed significant differences between the medium smokers and both the non-smokers and light smokers. Neither differences of blood levels of *total cholesterol* nor of *LDL* reached significance. *HDL* was significantly different between groups [$F(3,91) = 2.8$; $P < 0.05$] and the quotient *LDL/HDL* approached significance [$F(3,91) = 2.4$; $P < 0.1$]. No single post hoc test for either *HDL* or *LDL/HDL* reached significance.

Baroreceptor stimulation

Responses of heart period differed between baroreceptor manipulation conditions as revealed by a highly significant Condition effect [$F(3,97) = 280.6$; $P < 0.0001$]. In response to the baroreceptor stimulation, heart periods increased by an average of 46.8 ms and decreased by an average of 4.3 ms in response to control trials, compared

Table 1. Group means for age, weight, daily coffee consumption, home measured systolic and diastolic blood pressure and heart rate, weekly athletic activity, and blood lipid levels (total cholesterol,

LDL, HDL, LDL/HDL). Coffee consumption, blood pressure, heart rate and athletic activity values were obtained from diaries kept by the subjects

	Nonsmokers	Light smokers	Medium smokers	Heavy smokers
Age(years)	31.4 (6.2)	30.5 (6.6)	30.6 (5.3)	31.6 (4.7)
Weight (kg)	70.3 (14.7)	70.2 (10.8)	69.0 (14.5)	68.8 (13.4)
Coffee consumption (cups/day)*	2.7 (2.0)	3.1 (1.6)	4.4 (2.4)	3.6 (2.4)
Systolic blood pressure (mmHg)	116.9 (11.7)	118.4 (11.5)	117.1 (13.8)	119.3 (14.7)
Diastolic blood pressure (mmHg)	74.1 (8.7)	74.8 (7.1)	74.3 (7.7)	73.9 (8.0)
Heart rate (bpm)***	68.1 (10.9)	73.0 (7.6)	75.2 (8.1)	79.2 (7.4)
Athletic activity (min/week)	109.5 (145.5)	128.8 (181.0)	164.3 (190.0)	81.0 (116.8)
Baroreceptor sensitivity (Δ ibi)	44.1 (27.6)	61.8 (34.1)	50.8 (30.0)	52.8 (31.1)
Total cholesterol (mg/dl)	205.2 (42.3)	194.9 (29.2)	197.9 (35.7)	217.1 (40.6)
LDL (mg/dl)	107.5 (39.5)	113.4 (29.8)	121.1 (36.4)	133.4 (34.8)
HDL (mg/dl)*	62.3 (22.3)	51.8 (10.9)	52.2 (12.0)	53.4 (10.2)
LDL/HDL	1.9 (1.0)	2.3 (1.0)	2.5 (1.1)	2.7 (1.2)

*** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$

to their respective pre-trial baselines. Figure 1 shows the heart interval responses to both conditions. Neither the Group effect [$F(3,97) = 1.3$; $P < 0.1$] nor the interaction Condition $\times$ Group [$F(3,97) = 1.4$; $P > 0.1$] reached significance.

Nociception

Neither the Group [$F(3,99) = 0.3$; $P > 0.1$] nor Condition [$F(1,99) = 1.3$; $P > 0.1$] effect reached significance, but, as predicted, the interaction Group $\times$ Condition was significant [$F(3,99) = 3.1$; $P < 0.05$]. Post hoc tests revealed that in the group of heavy smokers, pain ratings were lower during baroreceptor stimulation as compared to the control condition ($F = 7.3$; $P < 0.05$). Figure 2 illustrates the effect. In the other groups, the two conditions were not significantly different.

Fig. 1. Grand mean of heart period responses to the baroreceptor stimulation condition (solid line) and the control condition (dashed line). The arrows indicate the beginning (S on) and end (S off) of the cuff pressure manipulations

Fig. 2. Subjective magnitude estimates (mean, standard errors bars) during both baroreceptor manipulation conditions, separated for the smoker groups. (□) Baroreceptor stimulation; (▨) control condition

Discussion

The aim of the present experiment was to investigate whether subjects show effects of artificial baroreceptor stimulation on pain perception depending on their daily smoking behavior. It was hypothesized that subjects who smoke, particularly those who smoke heavily, experience pain inhibition during intervals of increased baroreceptor activation. If this were true, it might be speculated that at least one rewarding aspect of smoking is the nicotine induced phasic increase in blood pressure which stimulates the baroreceptors and leads to decreased pain sensitivity and probably decreased general cortical arousal. The subjects investigated were divided into four different groups depending on their intensity of daily smoking. As expected, baroreceptor induced inhibition of pain was related to smoking habit: The group of heavy smokers showed less pain sensitivity during baroreceptor activation as compared to the control condition. This baroreceptor effect could not be statistically confirmed for any of the other three groups. Differential responses of heart period to both baroreceptor manipulation conditions were calculated as an index of baroreceptor sensitivity. For this measure, there was no significant difference between groups. For that reason, differences in baroreceptor sensitivity do not seem to be responsible for the observed pain inhibition effect in one group. Further analyses on data related to the cardiovascular system revealed that there were no statistically significant group differences for age, weight, systolic and diastolic blood pressure, athletic activity, total cholesterol, LDL and LDL/HDL. There was, however, a significant group difference of home measured heart rate indicating that non-smokers had lower heart rates as compared to all smoker group. This is in line with previously reported results (Benowitz et al. 1984). Additionally, groups differed in their HDL level. Post-hoc tests confirmed that the group of non-smokers had significantly higher HDL levels as compared to all three smoker groups. There was no significant difference between the smoker groups. Relationships between smoking habits and blood lipid levels have already been reported (Benowitz 1986) and are confirmed by the present result. The fact that there was no significant difference in HDL level between the three smoking groups does not support the speculation that levels in blood lipids are primarily responsible for the observed baroreceptor induced pain inhibition which was observed only in the group of heavy smokers.

The three smoking groups did not differ significantly in their number of years of smoking, and the four groups had no significant age or weight difference, but there was a difference in coffee consumption: subjects in the medium smoker group consumed significantly more coffee as compared to the group of non-smokers and light smokers. Given that it was the heavy smokers who showed a significant baroreceptor mediated antinociception effect, the differences in coffee consumption do not appear meaningful.

The present result show pain inhibition during periods of enhanced baroreceptor activity in heavily smoking subjects. None of the other measures, including blood lipid data, blood pressure, weight, and age, paralleled

these group differences. For that reason, it seems unlikely that one of these variables was responsible for the group differences in the observed baroreceptor effect.

Three independent studies (Elbert et al 1988; Rau et al. 1992, and the present experiment) have shown that factors which describe a risk for development of cardiovascular disorders (high tonic blood pressure levels, cigarette smoking, and positive outcome in the ergometer test) are related to the amount of baroreceptor induced pain inhibition.

One way to understand the result of the current experiment is to consider pain as only one form of aversive experience, and to view heavy smokers as a group especially eager to avoid aversive experience. Their psychological set may prepare them for both a high level of smoking behavior (which dampens cortical arousal) and readiness to exclude unpleasant experience, including pain, from awareness. In this model, their seeming lower level of tolerance for discomfort is offset by a higher sensitivity to the soothing effects of baroreceptor stimulation.

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