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Subjective and Brain-Evoked Responses to Electrical Pain Stimulation: Effects of Cigarette Smoking and Warning Condition[1]

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KNOTT, V. J. AND D. DE LUGT. *Subjective and brain-evoked responses to electrical pain stimulation: Effects of cigarette smoking and warning condition.* PHARMACOL BIOCHEM BEHAV **39**(4) 889–893, 1991.—Infrahuman studies employing behavioral indices of pain reactivity have supported a central antinociceptive action of nicotine which appears to be selective and dependent on the class of pain elicited. Human investigations employing subjectively based ratings and judgments of pain intensity have been less conclusive regarding the painfulness of stimuli following nicotine/smoking administration. As the more objective brain-evoked potential (EP) measure has been shown to reflect pain intensity and to be sensitive to a variety of analgesics, this study attempted to examine, together with subjective responses, the effects of cigarette smoking on EPs to pain stimuli administered under varying warning conditions. Twelve male and twelve female smokers served as experimental subjects. In smoking and nonsmoking sessions, subjective intensity ratings (SR) and vertex EPs were assessed in response to electrical skin stimuli presented at a level 20% above pain threshold. Stimulation was either nonwarned or warned with warning conditions involving single or repeated presentations of electrical current at constant or increasing intensities 12 seconds prior to pain stimulation. SRs and peak-to-peak N_1–P_2 EP amplitudes were measured for each smoking session and warning condition. A significant condition effect was observed for SRs with increasing prepain warning stimulation resulting in the greatest pain ratings. Although smoking did not directly alter SRs or EPs to pain, smoking exposure, as measured by carbon monoxide, was found to be differentially correlated with EP alterations in male and female smokers depending on the warning condition.

Smoking Pain Brain-evoked potential Subjective response

THE acute administration of nicotine in animals has been shown to exert relatively potent central antinociceptive actions in a variety of pain tests (1, 13–15, 19, 23, 29). Smoking/nicotine administration in humans, on the other hand, has not resulted in consistent antinociceptive effects, as some studies have reported no differences between smoking and nonsmoking states in pain "tolerance" thresholds (17, 25, 28, 31) while other studies have shown increases in pain "awareness" thresholds (5,20) and dose-dependent increases in pain "tolerance" thresholds (18,24). These findings raise the possibility that smoking/nicotine may selectively alter sensitivity only to certain components (i.e., physiological vs. psychological) of pain and/or classes of pain stimuli.

A number of smoking/nicotine studies have employed cutaneous electrical pain stimulation which produces a sharp and sudden rise in pain, the onset of which precludes any attempts by subjects to "control" their response. Pain perception and tolerance are altered by affective and cognitive processes (33), and individuals can and do successfully self-initiate and employ psychological pain relief strategies (e.g., relaxation and pain-distraction) (2, 22, 26), which are apparently more efficacious with slow- rather than with fast-onset pain (16). Cigarette smoking has been interpreted as a "psychological tool" (27) because of its reported ability to control arousal/mood (6) and enhance attentional efficiency (32), and, as such, it may reduce experimental pain by facilitating coping strategies, especially to slow-rising "expected" pain with a "predictable" rate of pain increase (16). The present study attempted to examine this hypothesis by comparing the effects of smoking and nonsmoking in response to telectrocutaneous pain stimuli presented in both nonwarned and warned conditions and with the latter being preceded by both constant and increasing intensities of prepain electrical stimulation. To determine whether smoking effects were central, and to objectively assess whether subjects might be actually "feeling" and not simply "reporting" altered pain sensitivity, scalp-recorded brain-evoked potentials (EPs) were employed as objective nocireactive response parameters along with self-reported pain intensity judgments. EPs have been shown to reflect the painfulness of stimuli (7) and to be sensitive to a wide variety of analgesic interventions, with the middle latency (N_1–P_2) EP amplitude being reduced by a range of prescriptive and nonprescriptive pharmacological compounds with varying potencies (3, 4, 21).

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METHOD

Experimental Subjects

Twelve male and twelve female smokers, responding to a newspaper advertisement, were selected for this study. All subjects were required to be free of CNS medications and to have no psychiatric history or history of substance abuse or neurological trauma/disease. The mean age of the male smokers was 23.3 (SD 3.1) and they had, on average, smoked for 7.3 (SD 3.0) years and were presently smoking a mean of 22.4 (SD 5.5) cigarettes/day. The mean age of the female smokers was 24.9 (SD 6.5) and they had, on average, smoked for 10.5 (SD 5.6) years and were presently smoking a mean of 24.7 (SD 7.2) cigarettes/day.

Study Design

Subjects attended the laboratory for one "orientation" session so as to familiarize them with study procedures and for two additional "test" sessions (separated by 1–2 days) during which subjective pain ratings and EPs were recorded following a smoking or nonsmoking period. The order of the test sessions was randomized so that half of the male and female subjects were tested in the cigarette smoking (CS) session first, and the nonsmoking (NS) session second, and the remaining half were examined in the reverse order. Prior to each test session, subjects were required to abstain from tobacco starting at 12:00 a.m. on the evening before the morning test sessions, occurring between 9:00 a.m. and 12:00 p.m. Subjects were also requested to refrain from alcohol and drugs for the same period of time. All measurements were carried out with the subjects sitting with eyes closed in a sound-attenuated, electrically shielded chamber adjacent to the control room housing the EEG amplifiers, computers, stimulators, recorders and video monitor.

Electrical Stimulation

Stimuli were generated by a Nicolet SM300 constant current stimulator which was capable of delivering monopolar rectangular pulses of various durations in the range of 0.05–39.0 mA with increments as low as 0.05 mA. Electrical pulses of 0.85-ms duration were applied to the tip of the index finger of the nondominant hand via a specially constructed gold-tipped isolated anode (diameter 1.0 mm) which was placed and properly fixed on an abraded site. The cathode was a Beckman miniature Ag/AgCl disc electrode placed on the middle finger, and a silver plate attached to the nondominant forearm served as ground. All electrode impedances were kept below 10 kohm.

Prior to each session, individual pain awareness thresholds were assessed by calculating the average mA level resulting from 5 separate "ascending methods of limits" series. Pain thresholds were found to be relatively constant for the subjects in both sessions, with the mean level in session one being 3.37 mA, while in session two it was 3.49 mA.

Four stimulus conditions were used in this study, and each involved the presentation of a pain stimulus (PS) which was set at a level 20% above each individual's averaged pain awareness thresholds. The four stimulus conditions are schematically shown in Fig. 1 and include the following: a) a Nonwarning Condition (NWC): entitled presentations of PS without any preceding warning stimuli; b) Single Stimulus Warning Condition (SWC): entailed presentations of PS with an electrical pulse (to the same finger), set at a level 80% below PS, preceding each PS by a 12-s period; c) Constant Stimulus Warning Condition (CWC): entailed presentations of PS with four electrical pulses, set at a level 80% below PS and each separated by 3-s intervals, preceding each PS by a 12-s period (i.e., a single pulse occurs at 12, 9, 6 and 3 s pre-PS) and d) Graded Stimulus Warning Condition (GWC): entailed the same stimulus parameters as CWC except that intensities of the pre-PS pulses gradually increased with the first pulse being 80%, the second pulse 60%, the third pulse 40% and the fourth pulse 20% below the PS level. During the test sessions, each condition was delivered 12 times, in a random order, with interstimulus (PS) intervals varying between 5–15 s.

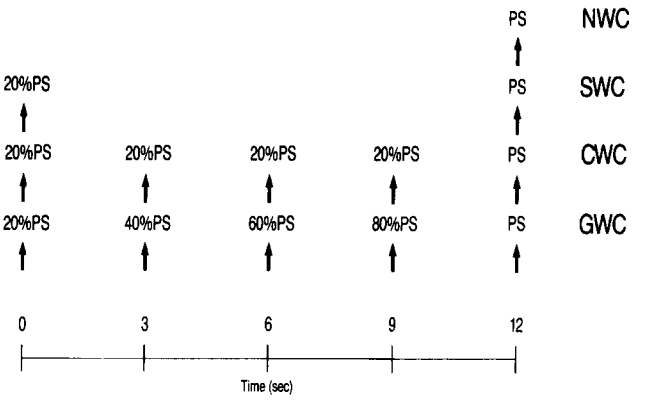

FIG. 1. The four pain conditions, as described in the text, included a nonwarning condition (NWC), a single stimulus warning condition (SWC), a constant warning condition (CWC) and a graded warning condition (GWC). Warning stimuli consisted of electrical pulses presented as a percentage (%) of the pain stimulus (PS).

Subjective Responses

Five hundred milliseconds after each PS stimulation, subjects were prompted with a free-field auditory tone which signalled them to verbally rate their subjective estimation of pain to that particular PS. Subjective ratings (SR) were carried out by reference to a scale ranging from 0–10 where 0 was defined as "no sensation" and 10 was defined as "unbearable pain" and values of 4 or more denoted increasing pain. Verbal ratings for the 48 (4 conditions × 12 trials/condition) PS presentations were transmitted from the subject to the control room by an intercom speaker.

EP Responses

EPs were constructed by separately averaging 12 post-PS EEG segments for each of the 4 different stimulus conditions in both NS and CS sessions. EEG was recorded with a miniature Beckman Ag/AgCl electrode placed, with paste, at the vertex (Cz) and referred to linked earlobes ($A_1 + A_2$). To avoid EEG artifacts by eye blinks/movements, electro-oculographic (EOG) activity was monitored with Ag/AgCl electrodes placed approximately 1 cm above and below the right eye in line with the subject's pupil. Both EEG and EOG were recorded with a band pass setting of 0.5–40.0 Hz, and averaging was carried out on line by directly feeding stimulus-locked EEG and EOG activity to an A/D converter which digitized both channels at 1000 Hz for a 1000 ms epoch from the beginning of PS onset. Epochs with EOG artifact (± 50 μV) were automatically eliminated from the averaging, and the separately averaged EPs for each condition were stored on disc for later off-line analysis.

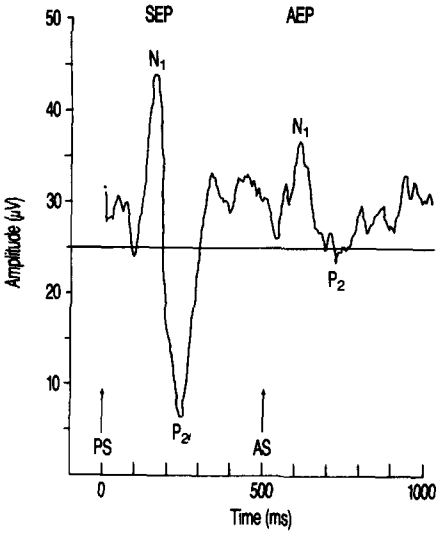

FIG. 2. Typical averaged brain-evoked potential (EP) recorded from a single subject during a nonwarning condition (NWC) without smoking. The electrical pain stimulus (PS) elicited somatosensory potentials (SEP) and the subsequent auditory stimulus (AS), for cuing subjective ratings, elicited auditory potentials (AEP).

Cigarette Smoking

Following electrode application and assessment of pain thresholds, subjects in the CS session were required to smoke, to completion, 2 cigarettes of their own brand within a 10-minute period. The mean tar and nicotine yields of the cigarettes smoked by the males were 13.8 (SD 1.2) and 1.1 (SD 0.12) mg, respectively. For the females, the mean tar and nicotine yields of their cigarettes were 12.9 (SD 1.3) and 1.0 (SD 0.08) mg, respectively. In the NS session, subjects were simply required to wait for the same 10-minute period. Smoke exposure was assessed before and immediately after the 10-minute period by sampling expired alveolar air and calculating (Ecolyser 2000) the carbon monoxide (CO) "boost" in parts per million (ppm) by subtracting presmoking levels from postsmoking levels. The mean CO boost in the CS session was 25.3 (SD 9.2) ppm, while the mean CO boost resulting from the NS session was −1.3 (SD 1.1) ppm.

Data Reduction

The 1-s post-PS epoch sweep allowed the capture of EPs to both PS and to the subsequent auditory stimulus used to cue SRs. Both the PS-derived somatosensory response (SEP) and the auditory response (AEP) were analyzed so as to determine specificity of smoking effects. The main components of each EP are shown in Fig. 2.

Amplitudes of EP peaks were identified by visual inspection and scored via a computer cursor program. As with previous algesimetric EP studies, only the peak-to-peak amplitude difference between the N_1 and P_2 components of the SEP were scored, and similar N_1–P_2 peak-to-peak amplitudes were scored for the AEPs. The subjective ratings in each session were separately averaged for each condition and subjected, as one value per condition, for further analysis.

Data Analysis

Each EP (SEP and AEP) and the SR measures were statistically analyzed by separate three-way [2 (Sex) × 2 (Session) × 4 (Conditions)] split-plot analysis of variances procedures (8), and any follow-up comparisons were carried out by *t*-tests. In addition, the relationship between response change in SR and SEP measures and the degree of smoke exposure was examined by correlating the "net" EP and "net" SR changes (i.e., CS minus NS values) with the "net" CO changes (i.e., CS boost minus NS boost values) using a linear Pearson regression statistic.

RESULTS

Figure 3 shows the mean pain ratings and grand averaged (i.e., averaged across males and females) EP waveforms for each of the four conditions in both NS and CS sessions. Analysis of SRs failed to yield any significant Sex or Smoking effects, but a significant Condition effect, $F(3,66) = 24.9$, $p<0.0001$, was observed with NWC resulting in the lowest pain ratings and the GWC producing the highest subjective pain responses. SEP analysis did not result in any significant main or interaction effects, but AEPs were significantly altered by Sex, $F(1,22) = 7.5$, $p<0.02$, Session, $F(1,22) = 7.1$, $p<0.02$, and Condition, $F(3,66) = 4.3$, $p<0.008$. Females were found to exhibit larger (mean 22.4 μV; SD 5.2) auditory N_1–P_2 amplitude than males (mean 17.6 μV; SD 5.3), smoking was shown to increase AEP amplitudes (mean 20.6 μV; SD 5.3) relative to nonsmoking (mean 19.2 μV; SD 5.2) and GWC resulted in larger AEPs (mean 21.3 μV; SD 5.9) relative to CWC (mean 20.4 μV; SD 5.6), SWC (mean 18.9 μV; SD 4.7) and NWC (mean 19.1 μV; SD 4.9).

Although changes in subjective ratings were not related to the degree of smoke exposure, significant SEP-smoke exposure relationships were observed under several stimulus conditions, and the direction of these correlations appeared to be dependent on sex. Interestingly, for females, all three significant SEP-smoke exposure correlations were positive such that SEP amplitudes were found to increase with increasing CO during NWC, $r(11) = .65$, $p<0.03$, CWC, $r(11) = .59$, $p<0.03$, and GWC, $r(11) = .63$, $p<0.03$, conditions. For males, the only significant correlation was a negative association with SEP amplitudes decreasing with increasing smoke exposure, $r(11) = -.62$, $p<0.04$, during NWC.

DISCUSSION

A previous attempt to examine the effects of cigarette smoking on electrocutaneous pain stimulation observed increased EP amplitudes following smoking (12). Although no direct smoking effects were observed with subjective pain in this particular study, intensity ratings, but not EPs, were found to be negatively correlated with smoke exposure. The present study failed to observe any significant smoking effects on EPs or SRs, and smoke exposure correlations were observed not with SRs but with only EPs, depending on condition and sex. Failure to observe direct smoking-induced antinociceptive actions on EPs or SRs during SWC, CWC and GWC warned conditions may be related to the "random" presentation of those stimulus conditions with the nonwarned condition. Psychological pain control stratagems have been found to be more successful under predictable-onset pain, and these processes and the effects of smoking thereon may have been partially blocked by intermittent presentations of nonwarned pain. Future attempts to design a paradigm to examine the impact of smoking on pain coping processes might attempt to randomly present "blocks" of each condition type so as to allow stabilization of self-initiated coping styles. Additionally, studies might attempt to examine the effects of smoking on pain response indices during implementation of experimentally induced

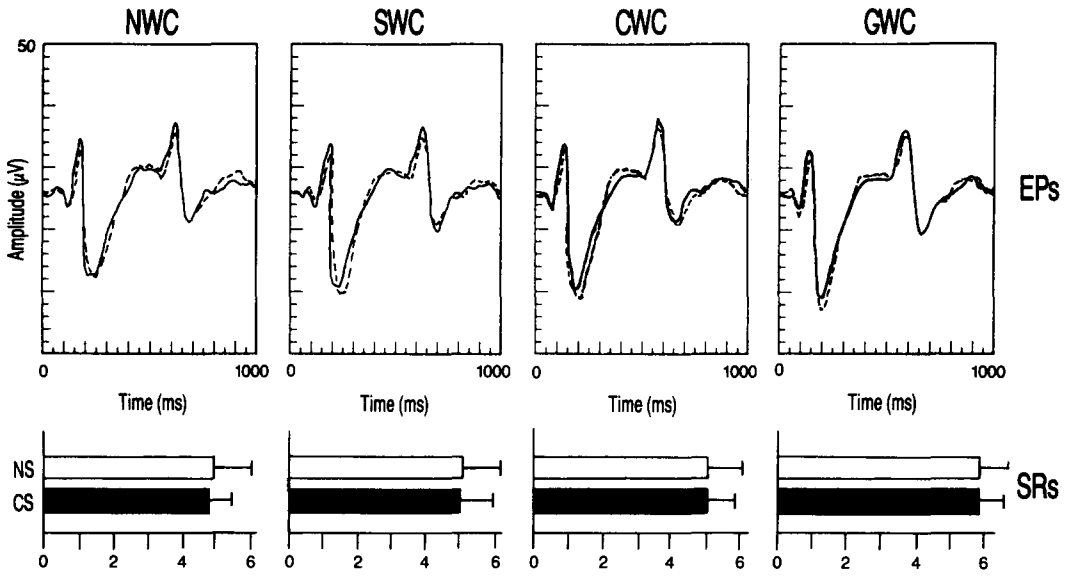

FIG. 3. Brain-evoked potentials (EPs) and subjective ratings (SRs). Grand averaged EPs and ratings are shown for each of the four pain stimulus conditions (NWC, SWC, CWC and GWC) in both nonsmoking (NS) and cigarette smoking (CS) sessions. Dotted lines = NS, and solid lines = CS.

coping stratagems such as relaxation training and distraction techniques and to compare the outcome of these manoeuvres in smokers with that in nonsmokers.

Cigarette smoking has been shown to exert a psychostimulant-like action on background spontaneous EEG (9,11), and the augmenting effects of smoking on auditory EPs in this study may reflect this general stimulating action. Previous smoking-AEP studies have indicated both depressant and stimulating actions on the auditory modality (10).

Greater subjective ratings in the GWC were paralleled by higher AEP amplitudes and, as such, both subjective and objective indices may reflect a greater conditioned emotional response to the overall higher electrical intensities inherent in the GWC condition. Failure to observe similar increases in somatosensory EPs may be due to a "ceiling" effect resulting from intense electrical stimulation. In females, however, EPs to electrical stimuli were found to increase with increased smoking exposure under certain warned and nonwarned conditions. In contrast, male smokers exhibited decreases in EPs to pain stimuli with increasing smoke exposure. Although these objective nocireactive indices were not associated with similar changes in subjective ratings, future research is required to determine the relevance of these findings to smoking motivation.

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