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Effects of Cigarette Smoking on Subjective and Brain Evoked Responses to Electrical Pain Stimulation

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KNOTT, V. J. *Effects of cigarette smoking on subjective and brain evoked responses to electrical pain stimulation.* PHARMACOL BIOCHEM BEHAV **35**(2) 341–346, 1990.—The effects of smoking two cigarettes on brain evoked potentials (EP) and subjective ratings (SR) of pain intensity to 3 levels of electrical skin stimulation were investigated in 14 female habitual smokers. Smoking increased EP amplitudes to all stimulus intensities, but did not alter SRs. Changes in SRs to intensities in the pain range, but not in the prepain range, were found to be negatively correlated with smoke inhalation as measured by expired alveolar carbon monoxide (CO) elevations. No significant EP-smoking inhalation correlations were observed.

Smoking Brain evoked potential Subjective response Pain Carbon monoxide Nicotine

ALTHOUGH a plethora of folklore and anecdotal literature have attributed analgesic properties to the tobacco plant and its active pharmacological ingredient nicotine (37), direct empirical support was not forthcoming until the early 1900's with the demonstration of sensocutaneous hypoesthesia following topical application of nicotine to cortical centres in dogs (2) and of nicotine-induced attenuation of experimental visceral pain in cats (20). A considerable number of infrahuman studies have subsequently attempted to examine antinociceptive actions of nicotine with a wide variety of pain tests. Although a few studies have reported null effects on pain thresholds (22,51), the majority of evidence has supported a central antinociceptive action of nicotine which appears to be selective and dependent on the class of pain elicited (1, 40–42, 48, 56, 63, 64).

The antinociceptive effects of smoking/nicotine in humans have been less conclusive. Several studies have produced results showing that pain tolerance does not significantly differ between nonsmokers and cigarette-deprived smokers or between smoking and nonsmoking states (46, 59, 62, 65). In sharp contrast to these findings, however, are reports indicating that: (a) nonsmoking smokers exhibit lower pain tolerance levels than nonsmokers (47, 57, 58, 60) and that (b) relative to smokers sham-smoking or smoking zero-nicotine cigarettes, smokers smoking low or medium nicotine yield cigarettes exhibit increased pain awareness thresholds (23,50) and dose-dependent elevations in pain tolerance thresholds which are comparable to or greater than those of nonsmokers (47,57). These antinociceptive effects have also been induced by the administration of snuff and appear to occur independently of the so-called 'nicotine-withdrawal' state as they can be elicited in ex-smokers as well as in minimally deprived, habitual smokers (23).

Although laboratory procedures for pain induction and assessment have varied considerably across smoking studies, they have, more often than not, employed subjectively based psychophysical ratings of 'awareness/tolerance thresholds' or 'intensity/magnitude judgements' of cutaneous pain as elicited by noxious mechanical, thermal, electrical and laser stimulation (27). These traditional techniques have been criticized for their methodological shortcomings (11, 12, 19, 43, 55), and advocates for a more objective algesimetric approach to pain assessment have promoted the concomitant use of scalp recorded brain evoked potentials (EPs) as suitable nocireactive response parameters (5, 13–15). The electroencephalographically (EEG) based EPs have been shown to reflect the painfulness of stimuli (9, 10, 16, 17, 29, 32) and to be sensitive to a variety of analgesic interventions with the pain-evoked middle latency (N_1-P_2) EP amplitude component being reduced by auditory analgesia (38), transcutaneous electrically stimulated analgesia (24) and a range of pharmacological analgesics (4, 6–8, 25, 30, 36, 61).

As EPs to painful stimuli have also been shown to be capable of discriminating weak analgesics with differing potencies (54), and to be responsive to nonprescriptive compounds such as aspirin (18), it was decided to examine whether smoking-induced pain relief could be documented by measuring both brain potential amplitudes and subjective ratings in response to painful and nonpainful electrocutaneous stimulation.

METHOD

Experimental Subjects

Fourteen female smokers, responding to a newspaper adver-

tisement, 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 group was 25.9 (SE = 2.0) and they had on average, smoked for 12.7 (SE = 1.5) years and were presently smoking a mean of 25.9 (SE = 2.3) 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 and EP responses were recorded following a smoking or nonsmoking period. The order of the test sessions was randomized so that half of the 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, all subjects were required to abstain from tobacco starting at 12:00 a.m. on the evening before the morning test sessions, occurring between 09:00 a.m. and 12:00 p.m. Subjects were also requested to refrain from alcohol and caffeine 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 which was immediately adjacent to the control room housing the computers, EEG and video monitors, stimulators and recorders.

Electrical Stimulation

Stimuli were generated by a Nicolet SM 300 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 msec 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 epidermal 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 KΩ. 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 same subject in both sessions [mean value across both sessions: 2.5 mA (SE = 0.61); Pearson product moment correlation coefficient r = .90; $p<0.01$]. The 3 different stimulus intensities used in this study were based on individual pain awareness threshold strengths (I_0) as determined at the beginning of each session: ($I_1 = 0.8 \times I_0$, I_0, and $I_2 = 1.2 \times I_0$) thus, for each subject one intensity level was in the prepain range and two were in the pain range. During the test sessions, each intensity was delivered 12 times, in a random order, with interstimulus intervals varying between 15 and 25 seconds.

Subjective Responses

Five seconds after each electrical stimulation, subjects were prompted with a free-field auditory tone which signalled them to verbally rate their subjective estimation of pain to that particular stimulus. Subjective ratings (SR) were carried out by means of an analogue scale ranging from 0 to 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 36 (3 intensities × 12 repetitions) stimulus presentations were transmitted from the subject to the control room by an intercom speaker.

EP Responses

EP's were constructed by separately averaging 12 poststimulus EEG segments for the 3 different stimulus intensities presented in each session. 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 artifacting by eye blinks/movements, electrooculographic (EOG) activity was monitored with Ag/AgCl electrodes placed approximately 1 cm above and below the left eye in line with the subject's pupil. Both EEG and EOG were recorded with a band pass setting of 0.5–40 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 500 msec epoch from the beginning of stimulus onset. Epochs with EOG artifact were automatically eliminated from the averaging and the separately averaged EP's for each intensity were stored on disk for later off-line analysis.

Cigarette Smoking

Following electrode application and assessment of 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 yield of the cigarettes smoked by this group were 12.6 (SE = 0.64) mg and 1.0 (SE = 0.04) mg, respectively. Subjects in the NS session 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' by subtracting presmoking levels from postsmoking levels. The mean CO boost resulting from the smoking period was 24.9 (SE = 3.3) ppm while the mean CO boost resulting from the nonsmoking period was 0.57 (SE = 0.6) ppm.

Data Reduction

The main components of a typical EP are shown in Fig. 1. 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 N1 component, occurring on average at 133.2 (SE = 4.5) msec poststimulus and the P2 component, occurring on average at 213.8 (SE = 7.8) msec poststimulus were scored. The subjective ratings of the 36 stimuli in each session were separately averaged for each intensity and subjected, as one value per intensity, for further analysis.

Data Analysis

Both EP and SR measures were statistically analyzed by separate two-way [2 (Session) × 3 (Intensity)] repeated measures analysis of variance (ANOVA; BMDP-2V) procedures and any follow-up comparisons were carried out by *t*-tests. In addition, the relationship between response changes and degree of smoke exposure was examined by correlating both the 'net' EP and 'net' SR changes (i.e., smoking minus nonsmoking values) with the 'net' CO changes (i.e., smoking CO boost minus nonsmoking CO boost values) using a linear Pearson regression statistic (BMDP-6D).

RESULTS

Figure 2 shows the mean and standard error values of the EP and pain ratings to the 3 stimulus intensities in smoking and nonsmoking sessions. Whereas analysis of EPs indicated a significant smoking effect, $F(1,13) = 22.9$, $p<0.0004$, with smoking acting to augment N1-P2 amplitudes to electrical stimulation across all intensities, smoking was found to have no effect,

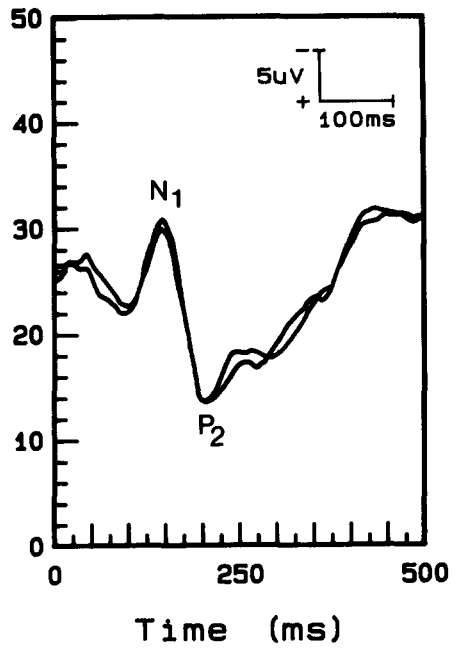

FIG. 1. Typical brain evoked potential (EP) response recorded from a single subject. The replicated waveforms were separately averaged in response to two runs of 12 electrical stimuli presented at pain threshold intensity with a varying interstimulus interval ranging from 15–25 seconds.

$F(1,13) = 3.4$, $p<0.10$, on subjective ratings to electrical stimuli. In contrast to these findings, correlational analyses, as shown in Fig. 3, revealed the presence of significant negative correlations between the relative change in smoke exposure and subjective pain ratings, but no significant relationship between the degree of smoke exposure and change in EP amplitudes. Further, as shown in Fig. 3, the negative correlations indicate that the relative decreases in pain ratings with increasing smoke exposure were restricted to electrical stimulation in the pain range only [I_0, $r(12) = -.65$, $p<0.02$; I_2, $r(12) = -.61$, $p<0.05$], and were not observed with prepain stimulation.

DISCUSSION

The present study observed a nonsignificant effect of smoking on pain sensitivity, but a significant effect on ERPs to painful and nonpainful stimulation. In contrast to smoking, CO did exhibit a relationship with pain, but it did not correlate with ERP changes. These results suggest, therefore, that smoking and CO reflect potent but different psycho-biological phenomenon, as do ERP and pain sensitivity.

Although smoking does not exert any overall effect on subjective pain, it appears that antinociceptive activity resulting from cigarette smoking may be dose-related and selective as pain ratings to electrical stimulation at and above pain awareness thresholds were found to be negatively correlated with the degree of smoke exposure as measured by expired CO. It may be argued that these effects may reflect a general 'relief' from the so-called 'withdrawal-state' and as such would not be demonstrated in naive,

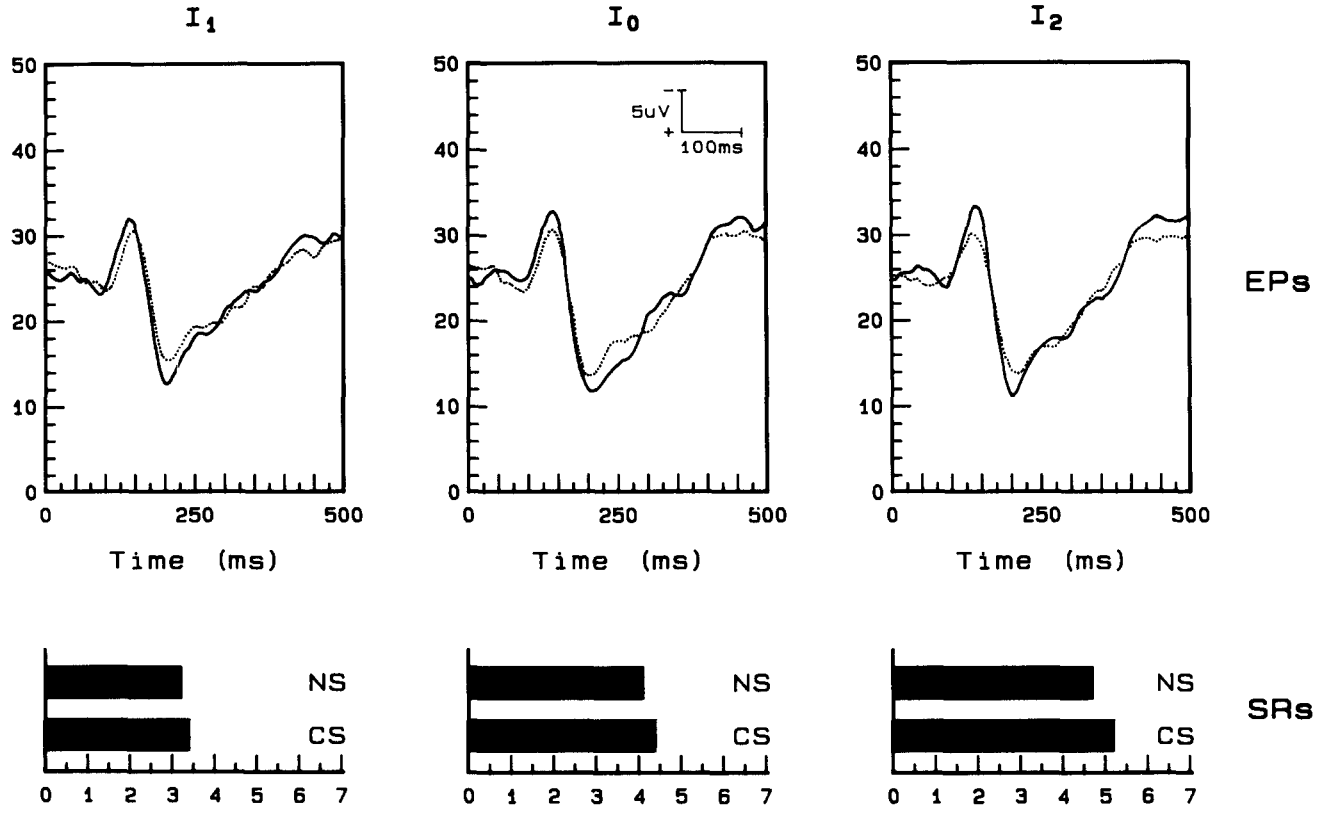

FIG. 2. Brain evoked potentials (EP) and subjective ratings (SR). Grand means are given over 12 stimuli per intensity (I_1, I_0, I_2; see text) and 14 subjects per treatment. Dotted lines = EPs in the nonsmoking condition; solid lines = EPs in smoking condition. NS = nonsmoking condition; CS = cigarette smoking condition.

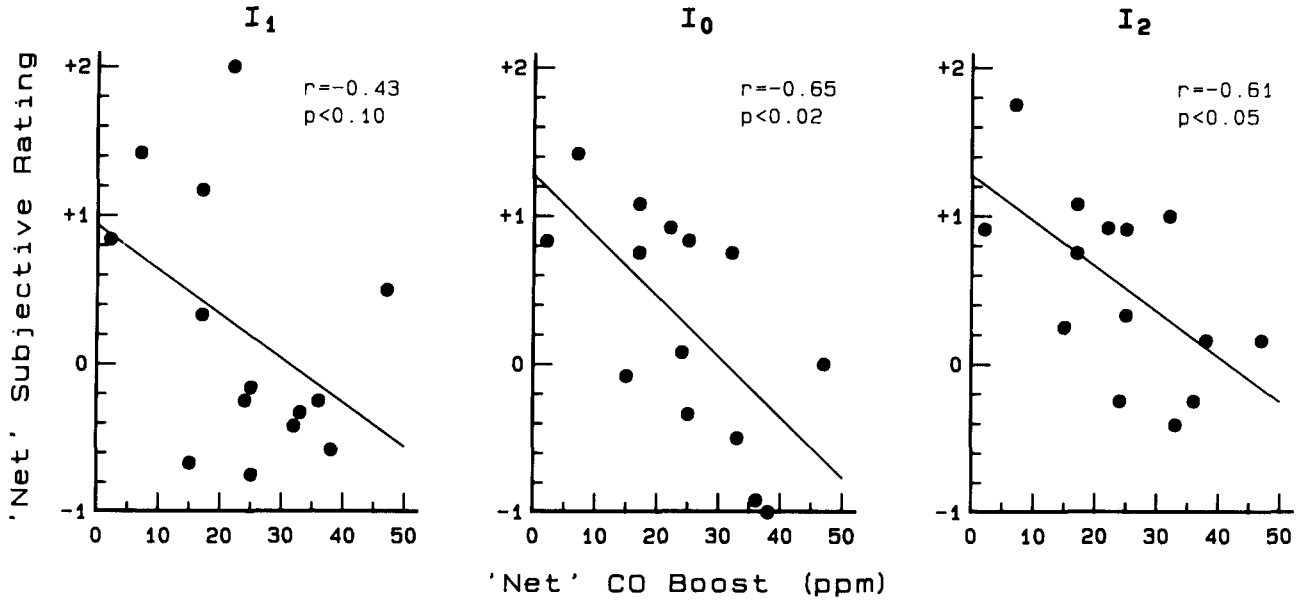

FIG. 3. Relationship between 'net' subjective pain intensity ratings and 'net' carbon monoxide (CO) boost (in parts per million, ppm) for each stimulus intensity (I_1, I_0, I_2; see text).

nonsmoker subjects. Fertig *et al.*'s (23) study seems to counter this view, however, as antinociceptive effects were observed both in ex-smokers and in minimally deprived smokers. Although further studies are required to determine the specific mechanism underlying this effect, it is within reason to suggest that the antinociceptive effect is induced by nicotine's action on the CNS. Nicotine exhibits a greater antinociceptive potency after central administration as compared to peripheral injections (41) and the time course of nicotine-induced antinociception correlates well with nicotine brain levels (64). Further, antinociception induced by nicotine is effectively blocked by the centrally active nicotine receptor antagonist mecamylamine, but not by the quaternary nicotine blocker hexamethonium which does not pass readily into the brain (56). It should be noted, however, that the increments in CO and in blood nicotine following a single cigarette are poorly correlated (3) and that alveolar CO does not necessarily correlate with CO in plasma (28), and as such, the former may be an unreliable indicator of the level of nicotine circulating in brain tissue. Measurement of plasma nicotine levels, although an indirect measure of CNS nicotine levels, would be useful in further elucidating the role of nicotine in mediating smoke-induced reductions in perceived pain.

Smoking increased EP amplitudes to electrical stimulation at all intensities. This finding of apparent augmentation of brain responsivity is in direct contrast to the typical depressant action of known analgesics on EP amplitudes (13) and is in disaccord with studies which indicate that smoking dampens EPs to aversive (auditory) stimulation (35). These present findings raise the possibility that previous reports of smoke-induced antinociceptive action on electrical pain may be related to the indirect action of smoke on CNS arousal mechanisms, with nicotine producing a general stimulation which may result in a nonspecific activation of normal neuronal function (41). Supporting this conjecture is the consistent finding that both smoking and nicotine administration exert a tonic excitatory effect on brain electrical activity as evidenced by reductions in slow wave EEG and by increases in the dominant brain electrical rhythm (34,49). Alternatively, enhanced EP's may simply reflect a cortical epiphenomenon resulting from nicotine's action on single or multiple brain regions influencing excitatory and inhibitory control, thereby simultaneously activating both ascending excitatory pathways modulating cortical arousal levels and lower descending inhibitory paths modulating pain sensitivity. Interestingly, nicotine-induced electrocortical activation is known to be dependent on an intact mesencephalic tegmental region (21,33) and, both electrical and chemical stimulation of the central tegmental-lateral paraqueductal grey area, even before a potentially painful stimulus is administered, produces a significant analgesic effect which appears to be selective to noxious rather than nonnoxious tactile input (31, 39, 44, 52, 53).

The above neurophysiologic interpretations do not of course negate the possibility that the antinociceptive effects of smoking may be achieved by its action on interacting psycho-physiological processes. Both affective (e.g., relaxation) and cognitive (e.g., distraction) stratagems have been shown to reduce the magnitude of experimental and chronic pain sensation (45). Smoking, presumably via nicotine's effect on brain processes, is known to exert an anxiogenic action and to improve the focusing and sustaining of concentration (66). As such, smoking may conceivably enhance pain relief by facilitating coping processes such as distraction, i.e., to competing sensory-psychic stimuli, and/or self-induced relaxation, i.e., of the muscular or autonomic nervous system. The present study design was limited in that it focused exclusively on acute experimental pain stimuli at or around pain awareness thresholds. Response to intensities at this level are viewed as tapping the 'sensation' or 'physiological' component of pain while response to intensities approaching pain tolerance thresholds are seen as reflecting the 'reactive' or 'psychological' component of pain (26). Future attempts to examine the interacting psychophysiological mechanisms underlying pain relieving effects of smoking might wish to incorporate into their designs both awareness and tolerance threshold intensities and couch them within stimulus paradigms which vary the rise time of pain as psychological pain-relief strategies appear to be more efficacious with slow, rather than with fast-onset pain (45).

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