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Effects of Nicotine on the Visual Evoked Response

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WOODSON, P. P., K. BAETTIG, M. W. ETKIN, W. M. KALLMAN, G. J. HARRY, M. J. KALLMAN AND J. A. ROSECRANS. *Effects of nicotine on the visual evoked response.* PHARMAC. BIOCHEM. BEHAV. 17(5) 915–920, 1982.—The effects of smoking cigarettes differing in nicotine content (0.14 vs 1.34 mg/cigarette) on the peak-to-peak amplitude and peak latency of the human averaged visual evoked response (AVER) were measured in 10 male smokers after a 2-hr smoking deprivation period. The AVER was obtained under five different flash intensities. Eight different peaks were involved in the amplitude and latency measurements. The nicotine dosage and flash intensity factors both had significant effects on peak-to-peak amplitudes while only the flash intensity factor affected peak latencies. The general enhancement of peak-to-peak amplitudes by the 1.34 mg cigarette, relative to the 0.14 mg cigarette, indicates that the effects of cigarette smoking on the AVER are predominantly due to nicotine's psychopharmacologic action, as opposed to other elements in tobacco smoke or as opposed to nonpharmacologic mechanisms involving learning processes. Past research, on an electrophysiological and behavioral level, indicating that nicotine, as administered via cigarette smoking, may have enhancing and/or restorative effects on visual attentional processes in the quiescent smoker was supported.

Nicotine Cigarette smoking Visual evoked response Attention Humans

THE effects of cigarette smoking and smoking deprivation in humans, under passive, quiescent conditions, on the averaged visual evoked response (AVER) have been investigated [16, 17, 23, 41] in order to clarify the effects of smoking deprivation and resumption on the smoker's visual processing of a simple unpatterned diffuse light stimulus presented repetitively in a discrete on-off fashion. The conclusion to be drawn from most of these studies [16, 17, 23] is that smoking deprivation (12 and 36 hr) causes decreases, as compared to predeprivation baseline conditions, while smoking resumption (after 1, 12, and 36 hr deprivation) causes increases, as compared to deprivation conditions, in peak-to-peak amplitudes within the secondary response phase [7] of the smoker's AVER. Of these studies [16, 17, 23, 41], only one [23] looked at peak latencies which were found to be unaffected by smoking deprivation and resumption. None of these studies [16, 17, 23, 41] however, tried to separate out the effects of nicotine or its metabolites [10, 32, 42] on the AVER from those due to other elements in cigarette smoke [10, 32, 42]. The only attempt [16] in this direction compared the effects of true smoking with tobacco cigarettes to that of placebo smoking with cigarettes made of roasted chicory leaves. However, such a placebo cigarette differs from the tobacco cigarettes, not only with respect to that of nicotine content but also, with respect to the composition of all non-nicotine substances. Furthermore, such factors as taste, odor, and draw resistance, which may play a role in the learned behavioral act of smoking per se, would also be expected to differ greatly between the tobacco- and chicory-leaf cigarettes.

The present study was undertaken therefore, to investigate the role of nicotine in the effects of smoking on the AVER by minimizing all possible differences between the experimental and control cigarettes. Toward this goal the experimental cigarettes, with 1.34 mg nicotine content, and the control cigarettes, with the pharmacologically inactive nicotine content of 0.14 mg [10,36], were similarly prepared and made of the same tobacco material. Therefore, they were equated for total particulate matter (TPM), FTC tar (i.e., as defined [32] by the U.S. Federal Trade Commission), H_2O content, and number of machine puffs. The effect of smoking these two cigarettes on the AVER was recorded

using five different flash intensities. The AVER parameters measured were peak-to-peak amplitude, as in the earlier studies [16, 17, 23, 41], as well as peak latency. Such measurements were made for the primary surface positivity (i.e., CD) [9,13] as well as for peaks within the primary- (i.e., I–III) and secondary-(i.e., IV–VII) response phases [7,13] of the AVER. This more detailed analysis, especially of the earlier components, was made possible through the use of a wider frequency filter bandpass which made for the incorporation of the higher frequency components of the AVER. When reported, the previous studies [16, 17, 23, 41] tended to use much lower low pass frequency filter settings.

METHOD

Subjects

Ten male clinical psychology graduate students, between the ages of 20–30 yr, served as subjects. Males were used since the females' menstrual cycle affects their electroencephalogram (EEG) [12]. All were inhaling smokers who had been smoking at least 20 cigarettes per day at the time of the study. A smoking history of at least 3 yr was required. Subjects were paid for participation in each of the two AVER sessions. Subjects were instructed not to smoke for 2 hr prior to each of the two AVER sessions. Subjects were informed that this experiment concerned the effects of smoking on brain processes.

Apparatus

Experimental cigarettes. The two experimental cigarettes, as prepared by Philip Morris USA, differed only in nicotine delivery (mg/cigarette: low delivery=0.14; high delivery=1.34). As they were similarly prepared and made of the same tobacco material, they were equal in TPM (mg/cigarette: low delivery=23.1; high delivery=24.2), FTC tar (mg/cigarette: low delivery=19.4; high delivery=19.4), H_2O content (mg/cigarette: low delivery=3.6; high delivery=3.5), and machine puff count (puffs/cigarette: low delivery=9.5; high delivery=9.3). Therefore draw resistance should have been similar. They were visually indistinguishable as well. The 0.14 mg cigarette is virtually equivalent to a placebo (i.e., no nicotine) tobacco smoking condition since it has been noted [36] that a 0.14 mg nicotine cigarette produced no pharmacological effect and produces blood nicotine levels (i.e., 8 μg/l) in inhaling smokers which were achieved by a noninhaler who smoked a cigarette of normal nicotine content (cf., [10]). Therefore, the 0.14 mg nicotine cigarette condition of this study constitutes an impure placebo [15].

With regard to the ability of the subjects to subjectively discriminate between the two cigarettes, an operant discrimination study [27], with autonomic nervous system measures (i.e., heart rate and finger skin temperature), has been conducted with these cigarettes. It was found that subjects could discriminate between them. Peripheral factors, such as the taste of nicotine in the 1.34 mg cigarette, may contribute to this discrimination, however animal work [34,37] indicates that the discriminative stimulus properties of nicotine are mediated by central nervous system mechanisms. No substantial pharmacological effects were found for the 0.14 mg cigarettes in this study [27] also.

AVER recording. The VER signal, during the recording session, was fed into a Grass P511 AC preamplifier which was powered by a Grass 107 regulated power supply. With regard to the frequency filter bandpass, the 1/2 amplitude high pass frequency filter setting was 0.1 Hz with the 1/2 amplitude low pass frequency filter setting being at 300 Hz. This bandpass has been found to be ideal for AER work [19]. The 60 cycle filter notch was out. A gain of 5.0×10^4 was used since it has been noted [6] that a voltage amplification from 5.0×10^3 to 5.0×10^4 is needed for computer analysis of bioelectrical activity as recorded from the scalp. After the signal had passed through this analog signal conditioner, the analog signal was fed into a voltage controlled oscillator (VCO) which converted the analog voltage signal into a frequency signal where a +1 V would be converted to 2,400 Hz, a 0 V to 2,000 Hz, and a −1 V to 1,600 Hz. This voltage-to-frequency conversion enabled the signal to be stored on a Tandberg TCD-310 direct-recording cassette tape recorder. Stereo recording was employed with VERs and flash marker pips being stored on separate channels. The pips served as flash discharge markers which were needed during signal averaging. Each time the Grass PS22 photic stimulator delivered a flash, the external monitor of this photo stimulator fed a pip directly onto the Tandberg TCD-310 tape recorder, bypassing the preamplifier and VCO, and onto the Tektronix Type 502 Dual-Beam cathode ray oscilloscope (CRO) for monitoring purposes. After the AVER session was over, the frequency signal, as stored on the tape recorder, was demodulated back into the original analog voltage signal via a frequency-to-voltage converter and fed into a Sigma 6 computer along with the direct playback of the pips onto a separate channel. This made digitization of the analog signal (one sample every 2 msec taken simultaneously on each channel) and signal averaging possible. The Sigma 6 input low pass frequency filters for both channels were set at 250 Hz (−3 dB). The AVERs at each intensity for each subject were then permanently recorded in graphic form by a Matrix Printer/Plotter made by Versatec. Absolute scales for voltage (in μV) and time (in msec) were used. For a schematic overview of the entire AVER recording process, see Fig. 1.

Procedure

Nicotine dosage administration. The two different nicotine dosages, as administered via cigarette smoking, were presented, in a counterbalanced fashion, not less than 24 hr and not more than 1 wk apart. A VER session was recorded after each administration. The two repeated measures for each subject were gathered at the same time of day to control for diurnal variations in the AVER [25]. After the 2-hr smoking deprivation period, plasma levels of nicotine should have been negligible [14], however, not enough deprivation time would have elapsed for any substantial nicotine withdrawal symptoms to have set in which could be clearly characterized as pharmacological in nature [38].

The VER recording session proper, which lasted about 5.7 min, started after a 6 min adaptation period which began after the subject had finished smoking the experimental cigarette. Accordingly, nicotine concentrations in brain tissue should have been in the maximal range during the VER recording session since whole-brain, nonspecific nicotine reaches a maximal level at 12 min postadministration (IP) in rats [37].

Experimental session protocol. Upon arrival at the laboratory, the subject was seated in a reclining chair in the test room which was humidity and temperature controlled. A gold-cup recording electrode was then affixed to the vertex (C_z) according to the International Ten-Twenty System of

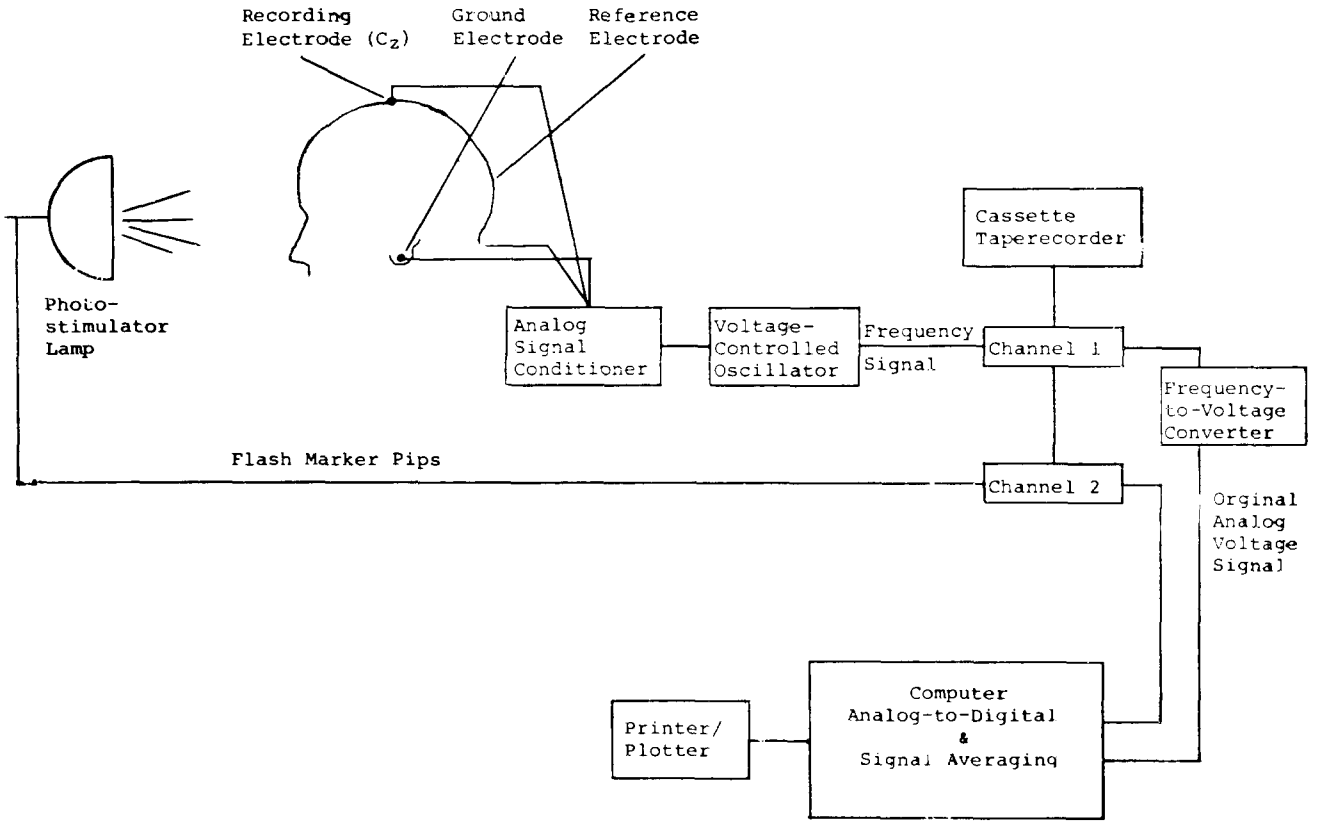

FIG. 1. Schematic overview of the AVER recording process.

Electrode Placement [24]. This recording site was chosen since the V–VI component (i.e., "vertex potential") is of maximum amplitude here [19]. The reference and ground electrodes were clamped onto the right and left ear lobes, respectively. Resistance was below 10 kΩ. After electrode placement, the subject was instructed on how to minimize myogenic artifacts and to gaze directly into the flashing light. The subject was also asked not to count the flashes to himself and to assume a passive attitude toward the flashes. After this instruction, the subject was given, in a double-blind fashion, one of the two experimental cigarettes, containing either 0.14 or 1.34 mg of nicotine, to smoke as the subject would a normal cigarette. The experimenter then left the room until the subject had finished the cigarette whereupon the experimenter returned and reclined the subject into a supine position in the chair. The testing room was then completely darkened by the experimenter who then went to an adjacent room where all VER equipment was located except for the flash lamp which was suspended directly above the subject's eyes. The subject then rested quietly in the darkened room for a 6 min adaptation period during which the subject was given feedback about myogenic contamination by the experimenter, who was monitoring the EEG on the CRO, in order for the subject to avoid such artifacts during the subsequent VER session. Fifty seconds into the 5th min of the adaptation period, the experimenter forewarned the subject that the photic stimulation would begin in 10 seconds. The pebbled Plexiglas face plate of the photo stimulator lamp was 50.8 cm from the subject's nasion with the axis of the flash lamp parabola intersecting the nasion approximately at right angles. At this distance, the light incident upon the eye has an intensity of 6.0×10^{-3} lumen-sec/cm^2 when the highest intensity of the photic stimulator is used. For a 10 μsec pulse, this corresponds to 1.9×10^{7} lumens peak intensity or Luminous flux at the point of origin [31]. The five flash intensities (i.e., 1, 2, 4, 8, and 16 relative intensities), subtending a nominal visual angle of 14.7°, were given in a random order with each intensity being given 64 times consecutively. This number of presentations per intensity was chosen since other studies [8, 17, 41] used similar numbers and it has been shown [19] that 16 presentations are enough to reveal the AER, with further presentations serving to improve signal resolution. Flashes were 1 sec apart with a pause of 3–5 sec being given between each intensity. The subject was told the flash stimulus presentation parameters prior to the VER session in order to reduce anxiety possibly due to uncertainty about the procedure.

AVER measurement. The AVER analysis involved the measurement of peak-to-peak amplitudes and peak latencies, for peak occurrence after flash discharge, for each subject's AVER to each of the five different flash intensities under each of the two different nicotine dosages. AVER peaks CD through VII were identified and measured blindly with regard to nicotine dosage. This peak nomenclature was adopted from previous work [7,13]. An AVER from the present study, with the peak locations, is shown in Fig. 2.

RESULTS

For the means±SEM (N=10), see Fig. 3 for each peak-to-peak amplitude and Table 1 for each peak latency as a function of nicotine dosage and flash intensity.

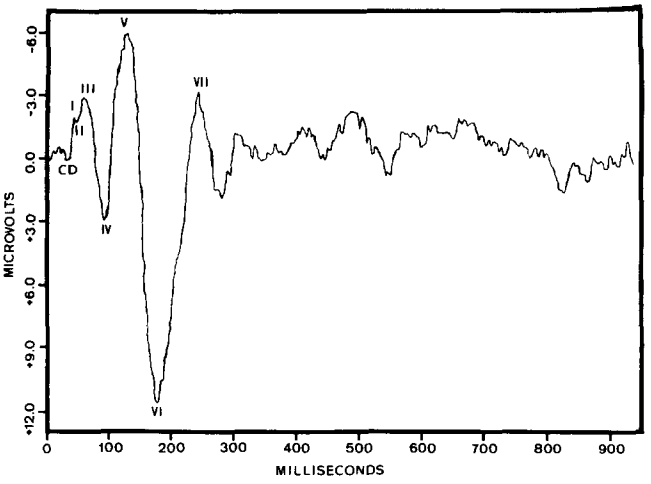

FIG. 2. An AVER from this study. For further explanation see Cigánek [7] and Creutzfeldt and Kuhnt [13].

Traditional two-factor (Dosage × Intensity × Subjects) Analyses of Variance (ANOVA) [28], with repeated measures on both the Dosage and Intensity factors for N=10, were performed for peak-to-peak amplitudes and peak latencies for each peak. In every case, Hartley's F max [44] showed homogeneity of variance ($p>0.05$) thereby permitting the use of these ANOVA tests. None of the ANOVA tests showed significant ($p<0.05$) Dosage × Intensity interactions. As can be seen from Fig. 3, nicotine (i.e., 1.34 vs 0.14 mg) generally tended to increase peak-to-peak amplitudes for all components at most of the intensities. However, this was significantly so only for component III–IV, $F(1,9)=5.54$, $p<0.05$. None of the peak latencies showed significant ($p<0.05$) differences due to the Dosage factor. Flash intensity significantly affected the peak-to-peak amplitudes of components CD–I, $F(4,36)=5.05$, $p<0.01$, I–II, $F(4,36)=4.15$, $p<0.01$, and III–IV, $F(4,36)=3.38$, $p<0.05$. As can be seen from Fig. 3, these peak-to-peak amplitudes tended to increase with intensities 1, 2, and 4 and then to level off for intensities 8 and 16. Flash intensity also significantly affected the latencies of peak III, $F(4,36)=8.25$, $p<0.001$, and peak IV, $F(4,36)=4.07$, $p<0.01$. From Table 1 it can be seen that these peak latencies tended to decrease with increasing intensity.

DISCUSSION

With regard to the effects of nicotine (i.e., 1.34 vs 0.14 mg), this study helps to clarify its role in the AVER peak-to-peak amplitude increases reported [16, 17, 23] after smoking resumption under quiescent conditions. Peripheral discriminative or conditioned stimuli (e.g., subjective cues such as the taste of nicotine), involved in the learned behavioral act of smoking, may also contribute to these amplitude increases, however such conditioned responses would seem to play a secondary role to that of central nicotinic actions (cf., [11]), with respect to smoking's effects on the AVER, in view of animal work [34,37] showing the discriminative stimulus properties of nicotine to be mediated via central mechanisms. With respect to the present study the fact, that the AVER recording began 6 min after the subject had finished smoking, would also tend to suggest that the amplitude increases are predominantly due to the psychopharmacological effects of nicotine.

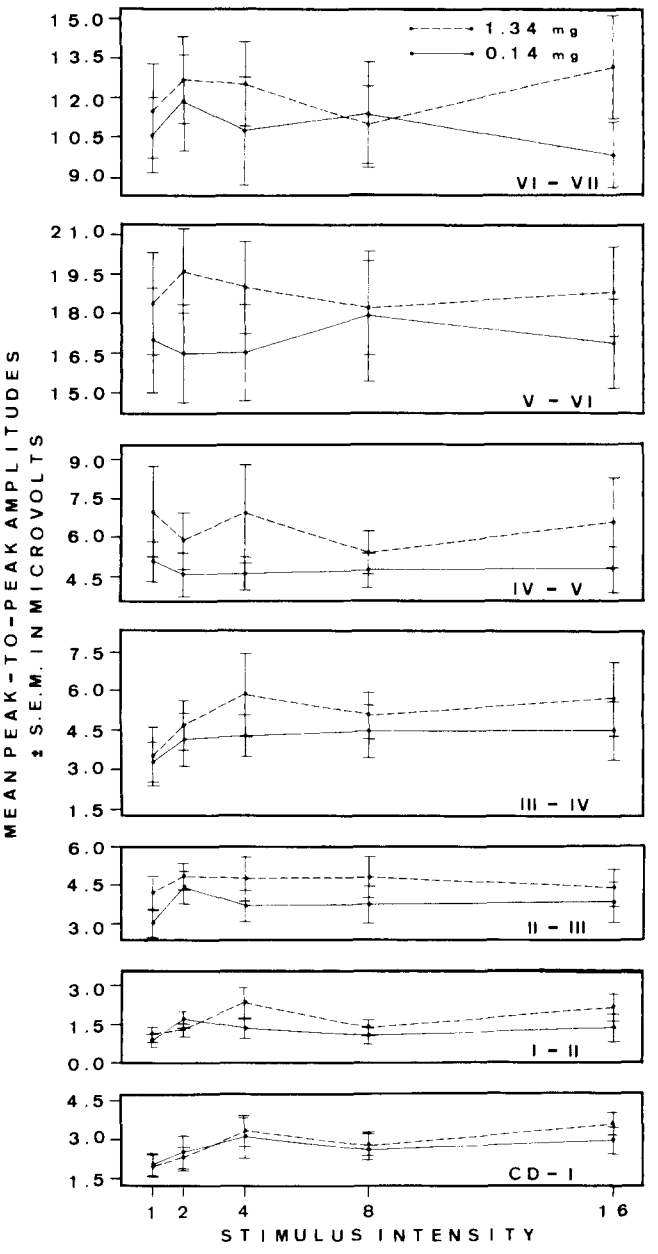

FIG. 3. Peak-to-peak amplitudes as a function of nicotine dosage and stimulus intensity.

With regard to the nature of the psychopharmacological mechanism by which nicotine does affect AVER amplitudes, research [8, 9, 20, 22, 39] on the AVER under nonpharmacological conditions shows the presence of visual attention or visual vigilance to affect peak amplitudes in a fashion similar to that of nicotine as administered via cigarette smoking. Peak amplitudes of the human AVER in general have been found (cf., [8]) to be larger under visual attention than under distraction. It should be noted that similar amplitude increases, as well as peak latency decreases, have been shown to occur with increases in flash intensity in this as well as in an earlier study [13]. This effect of visual attention has been demonstrated for a peak [9] within the primary response (i.e., peaks I–III, the electrogenesis of which is

TABLE 1

MEAN PEAK LATENCIES (±S.E.M. in msec) AS A FUNCTION OF NICOTINE DOSAGE AND STIMULUS INTENSITY

	Peaks							
Intensity	CD	I	II	III	IV	V	VI	VII
0.14 Dosage								
1	29 ± 4	45 ± 3	52 ± 3	74 ± 5	92 ± 5	114 ± 7	186 ± 8	281 ± 8
2	26 ± 3	39 ± 4	51 ± 4	71 ± 4	89 ± 5	111 ± 8	187 ± 8	290 ± 7
4	30 ± 1	45 ± 4	54 ± 4	69 ± 4	87 ± 6	107 ± 7	188 ± 11	290 ± 14
8	29 ± 1	42 ± 3	49 ± 3	68 ± 4	84 ± 4	108 ± 7	195 ± 10	285 ± 11
16	28 ± 2	40 ± 2	49 ± 4	66 ± 4	84 ± 4	110 ± 6	193 ± 13	291 ± 7
1.34 Dosage								
1	31 ± 2	42 ± 3	50 ± 3	71 ± 5	88 ± 5	114 ± 6	184 ± 6	282 ± 8
2	29 ± 3	42 ± 3	50 ± 3	70 ± 4	88 ± 4	112 ± 7	184 ± 9	288 ± 8
4	30 ± 2	42 ± 3	52 ± 4	68 ± 4	86 ± 5	110 ± 6	184 ± 10	294 ± 11
8	28 ± 1	41 ± 3	48 ± 4	65 ± 4	82 ± 5	111 ± 7	183 ± 10	292 ± 6
16	30 ± 2	42 ± 2	51 ± 3	65 ± 4	86 ± 5	111 ± 6	183 ± 10	300 ± 10

thought [7] to be due to specific pathway activation in area 17) as well as for peaks [20, 22, 39] within the secondary response (i.e., peaks IV–VII, the electrogenesis of which is thought [7] to be due to nonspecific, diffuse pathway activation) of the AVER. The results of this study show nicotine to affect both response phases in a manner similar to that of visual attention. It should be noted that attention has been distinguished from arousal [40] and that the general peripheral and central "arousal" effects of smoking doses of nicotine (cf., [11, 18, 26, 35]) alone are insufficient to account for the AVER amplitude increases which occurred after the 1.34 mg cigarette. For example, it has been shown [20] that merely arousing the subjects with occasional shocks had no effect on AVER peak-to-peak amplitude. In addition, smoking resumption has been shown [17] to increase AVER, but to decrease averaged auditory evoked response, peak-to-peak amplitudes. If the effects of nicotine on the AVER were due purely to a general central arousal, then amplitude increases should be observed for both the visual and auditory systems [16].

Similar parallels between the effect of smoking and the presence of visual attention can be found in the human EEG research. For example, smoking was found to enhance the alpha blocking effect of visual stimulation [33] as well as to increase the dominant alpha frequency (O_2 recording) in smoking deprived subjects [29]. This effect on alpha frequency was concluded to be due predominantly to the pharmacological action of nicotine (Herning, R. I., R. T. Jones and J. Bachman. *EEG alpha and tobacco smoking*. Manuscript submitted for publication, 1981.). Such a view is further supported by the observation [43] that the typical duration of these effects [29,33] of smoking is on the order of 20 minutes. This parallels the duration of the smoking-induced improvement on the critical flicker fusion (CFF) task [43] as well as the decline in whole-brain nonspecific nicotine after IP injection in rats [37].

Only one series of studies [2,3] has compared the effects of smoking and IV nicotine application on brain electrical activity. The amplitude of the contingent negative variation (CNV), which is positively related with attentional levels [40], was found [2] to increase with small IV nicotine doses (single shots totaling 12.5–50 μg) and to decrease with larger doses (single shots totaling 100–800 μg). Although a decrease rather than an increase occurred for the more normal (defined as 10–20 μg/kg IV, cf., [1,10]) smoking doses (i.e., 100–800 μg), this might, at least in part, have to be expected since the CNV task involved mainly auditory attention and it has been shown that smoking resumption in humans [17], as well as nicotine (12.5 μg/kg IP) in cats [21] depresses the peak amplitudes of the auditory evoked response. Nicotine in rats (12.5–100 μg/kg IP) also depresses the brainstem auditory evoked response [4]. These depressions in the auditory system parallel the finding [5] that nicotine (30–50 μg/kg IM) tends to elevate EEG and behavioral arousal thresholds to auditory test stimuli in cats. As has been previously suggested [17], this may indicate that nicotine has opposite effects on the two sensory systems. Similar opposing effects between the visual and auditory systems, in humans after smoking, have been reported [30] with respect to the Spiral After-Effect (visual) versus electrodermal reactivity to an auditory stimulus.

It may be tentatively concluded therefore, in view of the similar effects of visual attention and nicotine on the AVER, as well as the restorative and/or enhancing effects of smoking on various performance indices of attention (cf., [29,30]), that nicotine, as administered by tobacco smoking, may augment visual attentional processes in the quiescent smoker.

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