ELECTROPHYSIOLOGICAL EFFECTS OF THC ON CORTICAL SENSORY EVOKED ACTIVITY*

D. M. Wilkison

Department of Pharmacology and Toxicology
Medical College of Wisconsin
Milwaukee, Wisconsin

I. INTRODUCTION

A large body of information has been assembled which describes the effects of marijuana and its psychoactive components, the tetrahydrocannabinols. The investigations of the mechanism of action by which these compounds alter central nervous system function has proceeded in two complimentary directions, the neurochemical actions and the electrophysiological actions of cannabinoids. Studies on the electrophysiological actions of delta-9-tetrahydrocannabinol (THC) have produced information which suggest THC has actions in virtually every region of the CNS, cortex, limbic structures, hypothalamus, and spinal cord. The numerous effects of THC at these sites, both excitation and inhibition, have made generalized conclusions as to the neuronal actions of the cannabinoids elusive.

Since many of the effects of THC reported in man are related to changes in visual, auditory, and tactile perception (1,2), we are studying the effects of the cannabinoids on central sensory processing. Sensory perception is influenced by many factors beyond any specific sensory system. Subtle drug effects on perception may be the result of alterations in the integration of all sensory information. This could occur in central sensory area that receive multiple sensory information, i.e., areas outside classical sensory afferent pathways that respond to sensory stimulation in a nonspecific hetero-

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topic manner. Cortical sites that have such nonmodality specific representation have been described in cats (3-6). These areas receive afferent sensory information from thalamic nuclei, which also exhibit multisensory activity through pathways that are, in part, parallel to the primary sensory pathways, and many neurons in these areas individually respond to more than one sensory modality (7). A systematic exploration of the electrophysiological effects of the cannabinoids on sensory-evoked activity provides necessary information on the site of action of THC and the processes of sensory perception that are affected by THC in particular and, more generally, by the wide class of compounds that alter sensory function.

Other investigators have studied the effects of THC on sensory-evoked and electrically-evoked activity in sensory areas of the CNS. Low doses of THC generally increased cortico-cortical evoked responses whereas high doses of THC were found to be depressant. Auditory-evoked potentials also were enhanced by THC in the restrained, conscious cat. This was accompanied by an increased latency and broader peak of the evoked potential (8).

Thus, we have compared the effects of THC and a synthetic analog of THC, dimethylheptylpyran (DMHP) on visual and somatosensory evoked potentials in areas which are modality specific and in areas which receive multimodality information.

II. METHODS

Cats of both sexes, 2.5 - 4.5 kg, were anesthetized initially with halothane, and the trachea and femoral vein were cannulated. Cats were then transferred to alpha-chloralose anesthesia, 70 mg/kg, and the halothane discontinued. Cannulae were placed in the descending aorta via the femoral artery to monitor blood pressure. Cats were placed in a stereotaxic frame and the cortex was exposed bilaterally. Rats were anesthetized with alpha-chloralose-urethane and the femoral vein cannulated prior to placement in stereotaxic frame.

Subdural cortical, Platinum-ball electrodes were placed on the primary visual cortex (area 18), the primary somatosensory cortex (area 4), and the anterior marginal association cortex. Subcortical recording and stimulating electrodes were placed stereotaxically according to the atlases of Jasper and Ajmone-Marsan (9), and Pellegrino and Cushman (10). Coaxial, insulated electrodes were made from 23 ga. stainless steel tubing and an insulated 0.01 inch stainless steel center element. They were positioned in the dorsal lateral geniculate nucleus (LGN) or ventral posterolateral nucleus of the thalamus (VPL) for recording evoked bioelectric activity. Coaxial electrodes

were placed in optic chiasm (OX) for stimulation of the visual system. Parallel stainless steel electrodes with a 1-cm (cat) or 3-mm (rat) pole separation were placed subdermally under the radial nerve for stimulation of the somatosensory system.

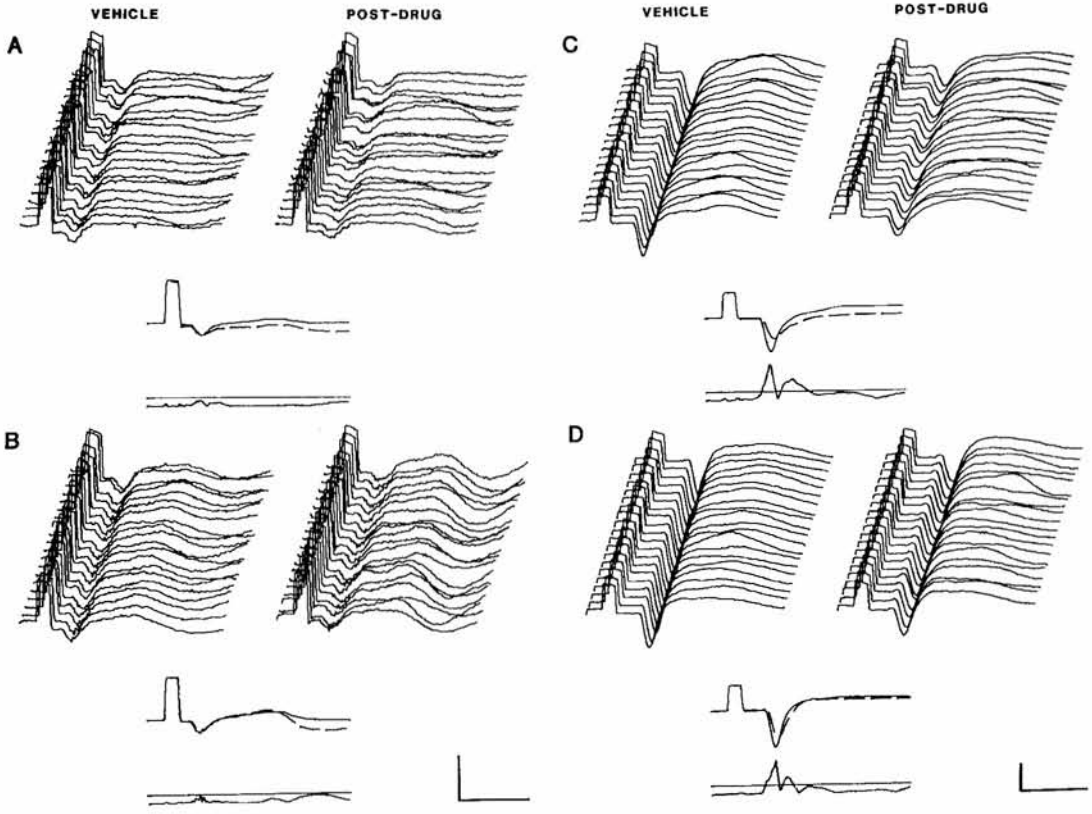
All cats were immobilized with a succinylcholine-saline drip, 1 mg/ml, and artificially ventilated to an end-tidal CO_2 level of 2.5-4.0%. Rats were allowed to respire spontaneously. Two to three hours elapsed after completion of surgery prior to the start of the experimental sessions. All recording sites were mapped to locate the site of maximal evoked potentials in response to stimulation of OX (0.05 msec., 0.5-1.0 mA), or radial nerve (0.5 msec., 0.05-1.0 mA), or both. The stimulus rate was once every four seconds (0.25 Hz).

Polygraphic records were made of end tidal CO_2, blood pressure, and bioelectric activity for cat studies. Rectal temperature was monitored and maintained between 36.5-37.5°C. Bioelectric activity was amplified with band-pass filters set at 3 and 3,000 Hz for primary cortical activity, 1.0-3,000 Hz for association cortex activity, and 3-10,000 Hz for deep nuclei activity. Electrical activity was either digitized "on-line" at appropriate rates and/or recorded on FM magnetic tape for subsequent processing.

Stimulus intensities were set as multiples of the threshold intensities required to elicit a primary cortical response for each sensory pathway. Experimental data was derived from responses evoked by stimulation of radial nerve at 1x, 2x, and 4x threshold or by stimulation of OX at 2x, 4x, and 8x threshold. Baseline and vehicle controls were established in each cat prior to drug administration.

At termination of the experiments, electrode sites were lesioned at 2 mA for 10 seconds and the brain perfused *in situ* with saline followed by 10% formalin saline containing 0.5% sodium ferrocyanide. Electrode sites were documented utilizing techniques described elsewhere (11).

Individual evoked potentials were digitized at appropriate rates (1,000-16,000 samples per second). Mean and standard deviations were calculated for each ensemble of 25 potentials. Latency-corrected mean, standard deviation, and standard error of mean of the latency and amplitude of the significant peaks of each potential were determined in order to characterize the ensemble. Drug effects were determined by the present change in amplitude of the evoked potential. Vehicle control effects were determined by comparing the 30-minute post-vehicle response to the pre-vehicle-baseline response. Responses after drug, 30-120 minutes, were compared to the post-vehicle responses. Thus, negative percent effects represented depression of the evoked potential amplitude and positive effects were facilitation. Significances of drug effect were determined by means of paired T-tests or analysis of variance.


VEHICLE
POST-DRUG
A
VEHICLE
POST-DRUG
C
B
D

THC and DMHP in 95% ethanol were dissolved in equal volumes of emulphor and diluted with water to 5 mg/ml. Vehicle consisted of ethanol substituted for drug.

III. RESULTS

In general, somatic activity was elicited by electrical stimulation of the radial nerve in cats and rats. The afferent somatic evoked activity was recorded from the contralateral primary somatosensory cortex and corresponding ventral posterolateral nucleus of the thalamus (VPL). Additionally in cats, somatosensory evoked activity was recorded from the anterior marginal association (AMA) cortex, a cortical site which receives multisensory information.

The positive wave of the somatosensory-evoked potential (SEP), recorded from the cortex of chloralose-anesthetized cats, was delayed by administration of THC (0.25-4.90 mg/kg) in a dose-dependent manner. Figure 1 illustrates the increase in the latency of the SEP elicited by radial nerve stimulation induced by 2 mg/kg THC. Somatic afferent activity at VPL was not significantly delayed (2 +/- 1.4%) by 2 mg/kg THC in 8 cats, which exhibited a 13 +/- 2% delay in the cortical response. THC depressed the amplitude of the cortical response only at the 4 mg/kg dose when moderate to high stimulation intensities were used. Responses to low, near threshold stimulus intensities were often depressed by THC such that detection and quantification of the response was not possible. These very small SEP to weak somatosensory stimulation were completely obscured in 5 of 12 cats. DMHP produced effects similar to THC but was more potent especially in depressing the amplitude of the cortical SEP. Figure 2 summarizes the dose response relationship for THC and DMHP on the cortical SEP in the cat elicited by electrical stimulation of the peripheral radial nerve.

FIGURE 1. Effects of THC on SEP at VPL and primary cortex. Individual SEP were simultaneously recorded from VPL (A,B) and primary somatosensory cortex (C,D) after vehicle (VEHICLE) and 30 minutes after 2 mg/kg THC (POST-DRUG). Potentials were evoked by two levels of stimulation: low (A,C) and high (B,D). Below each set of SEP are the superimposed averages, vehicle (-) and post-THC (--). Under each pair of averages the statistical T-values are illustrated, t = 7.5. Stimulation immediately followed calibration pulse, 5 msec, -500 mcV, positive voltage downward.

The relative lack of effect of THC on the somatosensory-evoked potential recorded in VPL suggested that the site of action for the cortical effects of THC may be either in the sensory processing and projection of information from VPL or in the integration at area 3 cortex itself. To distinguish between these two possibilities, cats were prepared as before except after the VPL and cortex were mapped the VPL was stimulated and the cortical SEP recorded. Figure 3 illustrates the effect of THC, 2 mg/kg, on the SEP evoked by stimulation of radial nerve or VPL and recorded at one cortical site. Stimulation of VPL evoked a positive wave on the cortex similar to that elicited by electrical stimulation of the radial nerve, albeit, with a shorter latency. THC produced similar effects on the cortical activity evoked from each site. The major effect of THC on cortical SEP as illustrated in Figure 3 was a slowing of the surface positive wave. This was most readily seen as the lengthened duration and increase in the latency of the peak. In five cats the latency of the positive wave was increased 10.8 +/- 1.5% for radial nerve-evoked and 12.1 +/- 2.6% for VPL-evoked responses.

Similar effects were observed in the cat anesthetized with chloralose-urethane and spontaneously respiring. The latency of the cortical potential evoked by electrical stimulationof the contralateral forepaw was increased following administration of THC in 5 rats (10 +/- 3.2%).

The effects of THC on the other sensory pathways were determined to evaluate the specificity of the action on the somatosensory system. In contrast to the effects on cortical SEP the visual evoked response to electrical stimulation of the optic chiasm was not altered by THC. However the auditory evoked potential did exhibit an increased latency after THC.

THC produced effects on sensory-evoked potentials in areas outside the classical sensory afferent pathways. The cortical association areas of the cat, in particular, anterior marginal which exhibits sensory evoked potentials from visual and somatosensory modalities in a heterotopic manner, was depressed by THC. In contrast to the primary sites, however, the visual-evoked activity recorded at the anterior marginal cortex was more depressed than the somatosensory evoked potential by 2 mg/kg THC (42 +/- 5.2% vs 21 +/- 8%) (Figure 4).

IV. DISCUSSION

Several studies on the effects of THC on sensory electrophysiology (8,12-14) in experimental animals and in man (2,15,16) have reported combinations of facilitation and depression and no effect. The absence of a unifying effect of

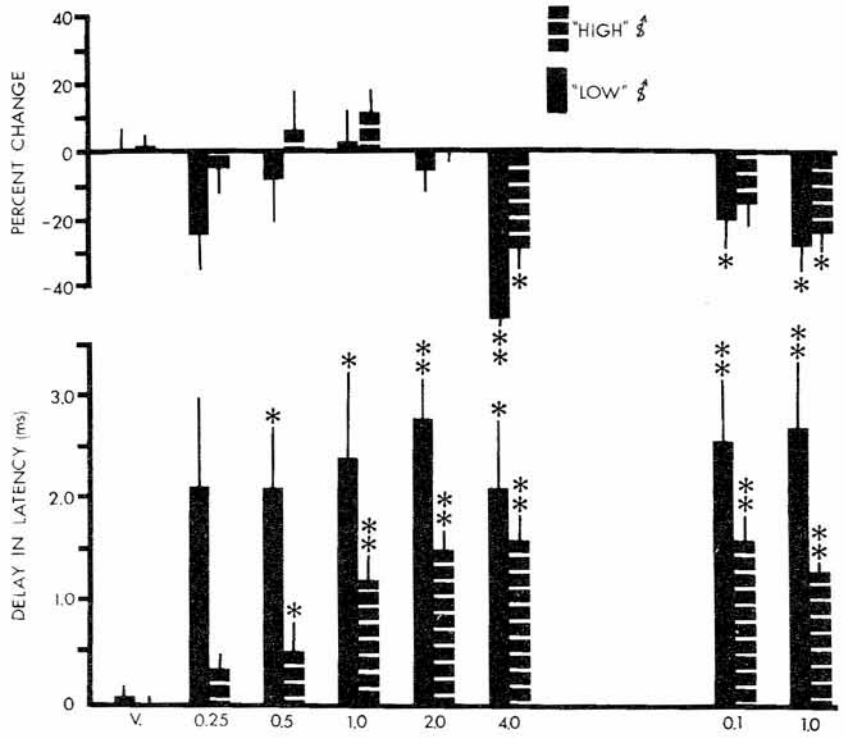
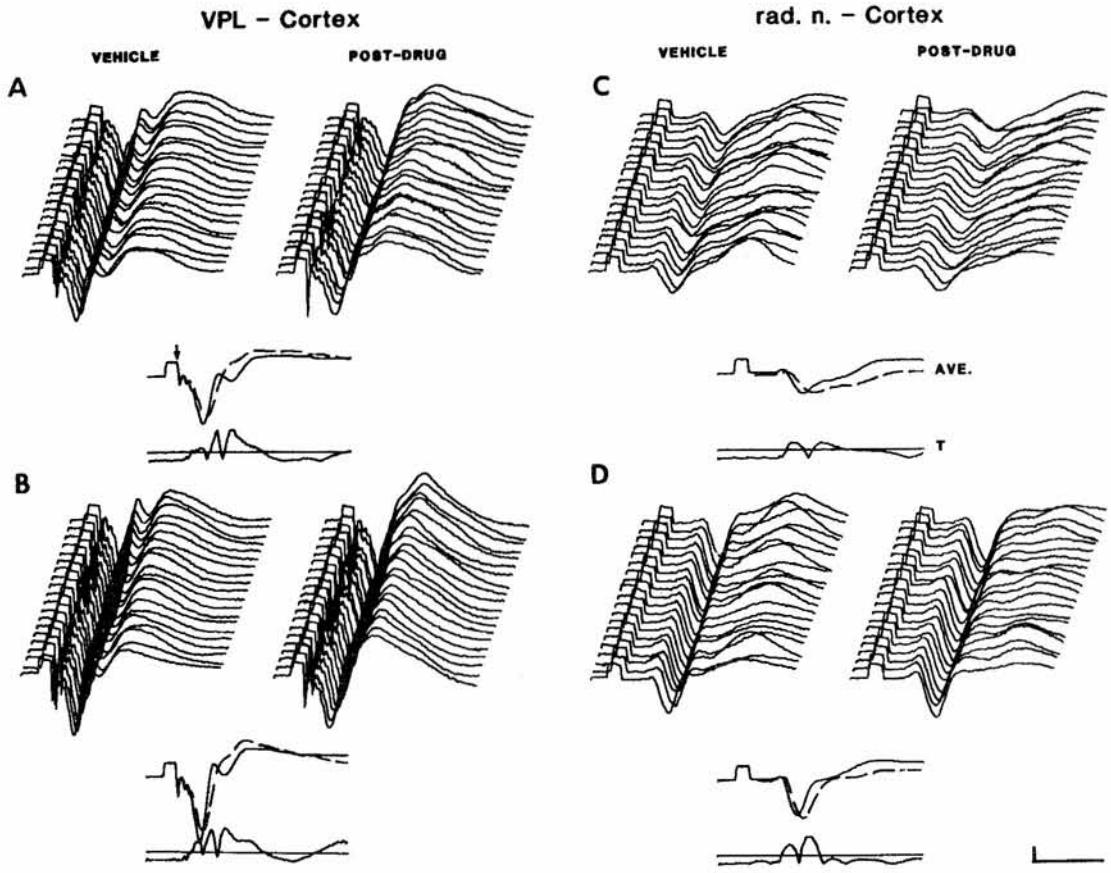


FIGURE 2. Dose-response effects of THC and DMHP. The effects of THC, 0.25-4.0 mg/kg, and DMHP, 0.1-1.0 mg/kg, on the primary SEP are displayed. Effects on amplitude (A) are displayed as percent change in peak amplitude and changes in latency (B) are expressed as the increase in latency. Data for low and high stimulus intensities are presented. (*, $p < 0.05$; **, $p < 0.01$)

THC on sensory activity in the CNS suggests that the actions of THC are dependent on the sensory modality and brain site. Dose, as well, can clearly alter the quality and direction of the effects of THC (17,18). Our present study, investigating three modalities of sensory perception in sensory-specific and convergent areas under the same conditions and often within preparation, supports the argument for specificity of action for THC.

In the chloralose-anesthetized cat the primary visual system appeared least sensitive to THC. The effect on auditory


VPL – Cortex
rad. n. – Cortex
VEHICLE
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VEHICLE
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A
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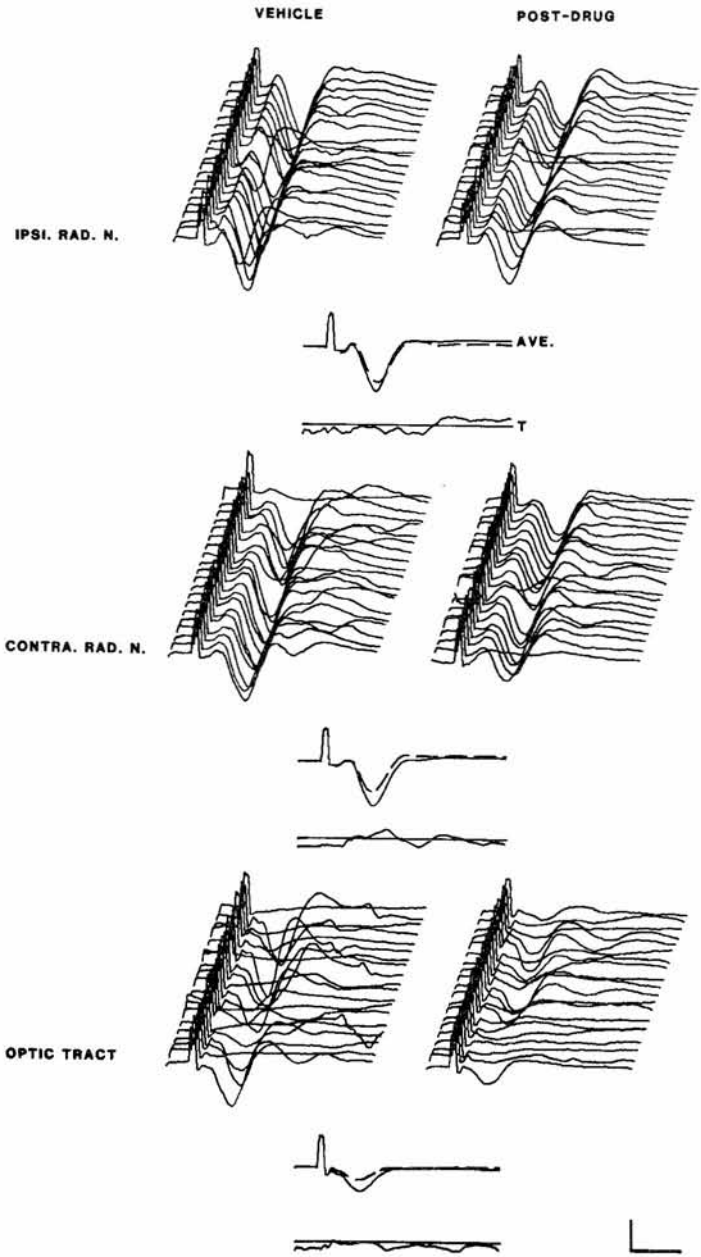
sensory potentials were in agreement with those reported by Guha and Pradhan (8) in restrained conscious cats. This similarity and the similarities between the cat and rat experiments in the present study indicates that the effects of THC were not unduely confounded by the alpha-chloralose anesthesia.

The slowing of the cortical SEP without significant alteration in VPL activity suggests THC may act to reduce cortical responsiveness in area 3. The greater effect on activity evoked by low intensity stimulation in comparison to high intensity stimulation suggests that THC increased the threshold for cortical activation or response in the somatosensory pathway. More coherent information, e.g., that evoked by stronger stimuli, may be less affected by THC. This hypothesis would account for the relative little effect on primary visual activity evoked by electrical stimulation of optic chiasm where transmission through LGN may maintain a greater degree of coherence activity than that along the longer multisynaptic somatosensory pathway.

Evoked potentials on the cortical surface are the reflection of slow potentials (EPSP's and IPSP's) in the anisotropic cortical layers (19,20). The positive and negative waves have been attributed to different cell-types in the cortical layers. The positive wave may arise from the afferent connections to the stellate cells (20-22). Towe (23) has identified a population of nonpyramidal cells in the somatosensory cortex of the alpha-chloralose-anesthetized cat which discharge in relationship with the positive wave. It is possible that THC may depress the activity of these stellate cells and/or pyramidal cells which do not extend axons through the pyramids thus slowing the cascade of synaptic events. Whether this action could account for the sensory-specificity or not requires further studies.

FIGURE 3. The effect of THC on primary SEP. Individual SEP were collected 30 minutes after vehicle (VEHICLE) and 30 minutes after 2 mg/kg THC (POST-DRUG). SEP were elicited by: low intensity VPL stimulation (A); high intensity VPL stimulation (B); low intensity radial nerve stimulation (C); and high intensity radial nerve stimulation (D). Below each set of SEP's are the superimposed averages of vehicle (-) and post-THC (--). Under each pair of averages a statistical "t" is displayed illustrating the magnitude of the difference of the average scaled by the pooled standard error, t = 7.5 is indicated. Electrical stimulation immediately follow the calibration pulse, 500 mcV, 5 msec. All responses were derived from the same cortical site. (from ref. 25, with permission.)


VEHICLE
POST-DRUG
IPSI. RAD. N.
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CONTRA. RAD. N.
OPTIC TRACT

Less functional detail is known about the cortical areas which receive multisensory information. However, multisensory neurons do predominate in these areas (6,24). In contrast to the relatively greater effect on somatosensory specific potentials over visual potentials, in the anterior marginal cortex the visual optic chiasm-evoked activity was depressed to a greater extent than activity evoked by somatosensory, radial nerve, stimulation. THC-induced alterations in activity in anterior marginal cortex may be the result of direct cortical effects or effects on subcortical, integrative thalamic regions that project to the association cortex. Additional data is needed to distinguish between these possibilities. Boyd and coworkers (12,13) reported enhancedcortico-cortical potentials after THC in the squirrel monkey. This finding is of interest because the cortical pathway studied was from primary somatosensory to association multisensory cortex. Although sensory evoked potentials in association cortex do not rely upon the integrity of the primary cortex, the potentials Boyd et al. (12,13) recorded may not be mediated entirely by the cortex. The evidence does suggest a facilatory action of THC in somatosensory elaboration to associative areas. The data presented in this report of a relative depression of visual information arriving at association cortex could be the result of such enhancement in the somatosensory pathways combined with a more generalized depression of sensory integration at either cortical or subcortical sites. A similar depression of association activity was observed after LSD (25) and may be involved in the sensory dissociation produced by drugs which alter sensory perception.

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FIGURE 4. Effects of THC on anterior marginal cortex. Potentials were evoked by stimulation of ipsilateral radial nerve (IPSI.RAD.N); contralateral radial nerve (CONTRA.RAD.N); and optic chiasm (OPTIC TRACT). Display is similar to Figures 1 and 3. All recordings are from a single cortical site. THC consistently depressed optic chiasm-evoked potentials more than radial nerve-evoked activity.

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