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Evoked Cerebral Responses to Noxious Thermal Stimuli in Humans*

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Summary. Brief pulses of Laser emitted radiant heat were used to induce cutaneous painful sensations in human volunteers. Accurate timing of the stimuli permitted recording of scalp averaged evoked potentials. A late negative-positive component of the EP which correlated in amplitude with the subjective sensation was abserved in four subjects. The latency of this component (130–160 msec) correlated with stimulus intensity.

Key words: Evoked responses – Pain – Laser.

Introduction

Attempts to record changes in cerebral activity following painful stimuli in man and animal were restricted to electrical stimulation of the tooth pulp (Chatrian *et al.*, 1975; Chin and Domino, 1961; Soto-Moyana *et al.*, 1966; Van Hassel *et al.*, 1972). We are not aware of reports describing evoked potentials to other types of noxious somatic stimuli. The requirements for such a method are several: Stimuli have to be very brief (several milliseconds) to permit time locking of EEG averaging to the sensory event; many repetitions of the stimuli without habituation are necessary for improving signal to noise ratio; only nociceptive fibers should be stimulated to avoid evoked responses to other concomitant sensations (e.g. touch, warmth).

Studies of the peripheral nervous system indicate that thermally sensitive nociceptors meet the last requirement. Some of these receptors respond only to temperature above 45° C, a temperature which inhibits ambient thermal receptors, and show only a slight degree of adaptation (Burgess and Perl, 1973). The methods commonly used for noxious thermal stimulation of the skin (the Hardy-Wolf-Goodel incandescent source or various infrared sources) are not suitable for recording evoked potentials to pain, since at their intensity pain thresholds are obtained in no less than 250 msec, a duration which is too long to permit accurate

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time locking for the stimulus event to the EEG. Concentration of thermal energy in minute time frames can solve this problem.

Methods

A new technique to induce thermal pain devised by the authors (Mor and Carmon, 1975) was utilized to record cerebral evoked potentials to noxious thermal stimuli. Very brief and intense pulses of thermal energy from high powered CO_2 Laser (Model C-8 Laser, Israel Electro-Optical Industries) produce a thermal or painful sensation which can be manipulated by changing intensity, duration or area of stimulation. Sensation ranges from warmth through slight pain to severe stabbing pain. Psychophysical studies with these stimuli showed absence of significant habituation or sensitization after more than 100 repetitions. This, in addition to the brief nature of the stimuli and the accurate timing, makes them suitable for recording of evoked potentials. The fact that most of the 10.6 μ infrared energy is absorbed in the outer 0.5 mm depth of the skin (Stellar *et al.*, 1974) suggests that only superficial receptors are stimulated at brief durations.

Four healthy students served as paid subjects. All were informed about the nature of the study, and that at noxious level a slight transient erythema might appear at the locus of stimulation. Special care was taken to avoid any risk to the subjects by using several safeguards (Mor and Carmon, 1975). The locus of stimulation was the lateral side of the right forearm.

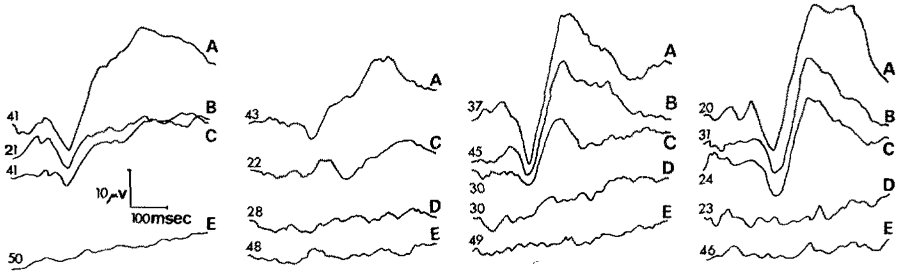
Initially, subjects were trained to categorize sensations on a subjective scale. Stimuli durations were 6–14 msec, depending on the intensity of the output. Thresholds were determined by the method of limits. With a focused beam (stimulus size 0.28 cm^2) threshold (as computed by integration of stimulus energy over time of exposure) was 120–130 $mCal/cm^2$ for slight pain, 160–170 $mCal/cm^2$ produced moderate pricking pain, and 200–220 $mCal/cm^2$ resulted in severe stabbing pain. The painful sensations were not associated with a subjective experience of a temperature rise. Warm sensations could be felt only when the skin was irradiated by a nonfocused beam (3.14 cm^2). Threshold for this sensation was around 30 $mCal/cm^2$ and was achieved by stimulation with low intensity Laser output for 36–42 msec.

A PDP 11/45 computer controlled stimuli and received the analogue input from the EEG. Averaging was done for periods of 500 msec following the onset of stimulation. Recordings were monopolar. Four electrodes were used: one electrode was placed at the vertex (C_z), one over the contralateral somatosensory cortex (C_3) and the third one over the ipsilateral somatosensory cortex (C_4) or over the contralateral associative somatosensory cortex (P_3). The fourth electrode was placed on the outer canthus of the eye. Trials in which gross eye movements occured were not recorded. In several instances the fourth electrode was placed on the right arm or forearm in order to detect peripheral electric changes or electromyographic responses. Electrodes on the two ears were connected for common reference. Subjective responses were recorded 2 sec after averaging was terminated. Subjects indicated their subjective sensations by pressing on a set of microswitches with the left hand.

Each subject served in two independent experiments in which (1) 35 non-noxious thermal stimuli applied with the nonfocused beam were used to trigger averaging of the EEG, and (2) averaged evoked potentials to noxious thermal stimuli of two intensities were recorded. In order to minimize expectancy, two levels of noxious stimuli (determined by psychophysical thresholds of slight pain and moderate pain) were randomized with blank trials. With false negative responses being recorded as well the number of averaged trials per condition varied between 20 and 50. The number of trials was determined also by subjective tolerance. The two experiments were repeated twice on each subject on different days.

Results

A typical evoked response was obtained in all subjects when noxious sensation was felt. Responses were easily replicable in each subject and a high degree of similarity was obtained between responses of different subjects. The largest ampli-



SUBJECTIVE RESPONSE	STIMULUS (mCal/cm²) 0	130	170
NONE	E	D	–
SLIGHT PAIN	–	C	B
MODERATE PAIN	–	–	A

Fig. 1. Vertex evoked potentials for combinations of two radiant heat intensities and three response levels. Records were obtained from four subjects. The number in the left-hand side of each trace indicates number of trials averaged. Positive deflection up, negative down

tude responses were recorded from the vertex. Contralateral and ipsilateral somatosensory evoked responses had amplitudes smaller by 20–40 % but shape-identical to the vertex response. Ipsilateral somatosensory responses were only slightly smaller than contralateral ones. No clear difference was obtained between recordings from C_3 and P_3.

The most typical response was a negative wave with peak latency of 130–190 msec followed by a very large positive wave with peak latency at about 230–300 msec.

The averaging of the EEG was done according to stimulus-response combinations. Since the intensities selected were at thresholds, the same stimulation could elicit different sensations. The 130 mCal/cm^2 stimulation was perceived as slight pain in some trials while in other trials it was not perceived at all. For the trials in which the subject was stimulated by the smaller intensity but had felt neither pain nor warmth, no evoked response was obtained (cf. Fig. 1D). The slow positive shift observed inconsistently in these trials can be attributed to resolution of a CNV. On trials in which the same stimulus intensity was applied and the subject reported a slight painful sensation, the typical evoked response was recorded (cf. Fig. 1C). The 170 mCal/cm^2 stimulation elicited mainly feeling of moderate pain. Sometimes, however, it resulted only in slight pain. At this stimulus intensity the response amplitude was larger when it was felt as moderate pain than when it was felt as slight pain (cf. Fig. 1A and B). The latencies for the stronger stimulus were shorter by about 10 msec than to the weaker stimulus.

In some of the records an additional feature was an early small double positive peak (P_{50} and P_{90}). This peak was missing in other records, and was not correlated to either the scalp locus or stimulus and response levels.

No replicable evoked response to stimuli which elicited warm sensation without pain was optained in our subjects. In two instances a rudiment of the negative wave could be detected. However, with this sensation, subjects felt sometimes also a slight "sting". Averaging from the peripheral arm electrode did not disclose any response associated with stimulation by the Laser beam.

Discussion

The results of the present study show that thermal stimulation by heat radiating from a Laser can elicit a very large and identifiable cerebral evoked response only when the stimulation was noxious and only when it resulted in a subjective experience of pain. The amplitude of the response is correlated with the subjective sensation, while the latency as defined by the initial negative component seems to be related to the stimulus itensity. When stimulation resulted only in sensation of warmth no evoked responses were recorded as reported by Duclaux *et al.* (1974). The shape of the late components of the voked response to pain resembles shapes obtained for other somatic stimulations (Barret *et al.*, 1974; Franzen and Offenloch, 1969; Goff *et al.*, 1969; Schmidt, 1970; Uttal and Cook, 1964), with a high amplitude positive wave around 200 msec preceded by a small negative wave, and which are mostly accentuated over the vertex. The latency of the evoked response is compatible with excitation of superficial myelinated nociceptors, which have conduction velocity of 4–10 m/sec, are slowly adapting and respond most vigorously to noxious heat (Burgess and Perl, 1973).

These late components are considered to be "non-specific", and possibly due to arousal. The fact that in the present experiment only stimuli which aroused pain were accompanied by the large late negative-positive complex supports this notion. It is possible that only the arousing and alerting effect of pain is responsible for the electroencaphalographic phenomenon observed. If true, then the evoked potential found in this study can be ascribed as an indicator of cerebral arousal which is due to pain.

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