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Cutaneous pain and detection thresholds to short CO_2 laser pulses in humans: evidence on afferent mechanisms and the influence of varying stimulus conditions

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Summary Pain and detection thresholds to short CO_2 laser pulses were studied in healthy human subjects. Pain thresholds were significantly higher than detection thresholds in both hairy and glabrous skin; in the glabrous skin both thresholds were higher in the hairy skin. The range from detection threshold to pain threshold was larger in the glabrous skin. The minimal energy per surface area needed to produce any sensation (detection) or pain sensation decreased with increasing stimulus surface, and this spatial summation effect was to equal magnitude in the hairy and the glabrous skin. With decreasing stimulus pulse duration (from 45 to 15 msec) the detection and pain thresholds were elevated: this effect was stronger on pain thresholds. With increasing adapting skin temperature, less energy was needed to produce any sensation (detection) or pain sensation. The effect of adapting skin temperature was equal on pain and detection thresholds. The conduction velocity of fibers mediating laser evoked first sensations was in the thin fiber range (< 10 msec), according to a reaction time study. The results suggest that short CO_2 laser pulses produce both non-pain and pain sensations, but that both these sensations are based on the activation of the same primary afferent fiber population of slowly conducting nociceptive fibers. Central summation of primary afferent impulses is needed to elicit a liminal non-painful sensation, and an increased number of impulses in the same fibers produces pain.

Key words: Cutaneous pain; CO_2 laser; Threshold; Adapting temperature; Reaction time; Central summation

Introduction

Mor and Carmon [28] developed a method for using short CO_2 laser pulses in pain research. One potential advantage of this method is that, unlike contact thermostimulators, lasers should not produce a simultaneous activation of mechanoreceptors. Furthermore, in contrast to the conventional radiant heat method [17], short laser pulses produce a synchronous volley of afferent impulses, allowing a simultaneous measurement of evoked potentials at different levels of the nervous system. Reaction time studies are also possible with short laser pulses. Since the development of this method, it has been used in several psychophysical [6,8,30] and the electrophysiological studies [4,5,7,11]. It has been shown that at the primary afferent level the short CO_2 laser pulses activate selectively the thin cutaneous afferent fibers in animals [11] and in man [4]. Evoked potential studies have demonstrated cerebral responses correlated with pain and mediated by thin myelinated [7] or unmyelinated [5] primary afferent fibers.

The problem limiting the more widespread use of short laser pulses in experimental and clinical

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pain research has been that until recently, the equipment needed to produce these stimuli was not only expensive but demanded extensive space, engineering expertise, and was not easily positioned. However, due to increasing application of lasers in surgery, more versatile, smaller, simpler-to-use, and also less expensive CO_2 laser devices have been developed. This development of new laser devices allows a more widespread use of CO_2 laser in pain research.

Because of the lack of data concerning the effect of varying stimulus conditions on CO_2 laser-evoked sensations, we wished to determine the thresholds of CO_2 laser-evoked sensory responses under different experimental conditions in healthy human subjects. The effect of skin region (hairy vs. glabrous skin), stimulus beam size, stimulus pulse duration and adapting skin temperature was studied using psychophysical threshold determination methods. A reaction time study was made to determine the conduction velocity of primary afferent fibers mediating laser-evoked sensations. We also determined whether non-painful and painful sensations produced by CO_2 laser pulses are mediated by a single population of afferent fibers.

Methods

This study was performed with 6 healthy subjects (5 males, 1 female) of 25–51 years. The subjects were members of the laboratory staff. An informed consent was obtained before the experiments. The experiments were done between 09.00 and 17.00 h. The subjects and the experimenters used protective goggles.

The Model 20 Carbon Dioxide Surgical Laser System (Directed Energy, Inc., Irvine, CA, U.S.A.) was used to stimulate the skin; this device has a hand-held laser head for directing the stimulus beam. The system generates a laser radiation beam in the infrared spectrum (10.6 μm wavelength). The system has adjustable power and pulse duration and is capable of producing peak laser powers of over 20 W. Because the system is primarily developed for use in surgery, the laser beam is focused about 3 cm in front of the laser head. The stimulus area can be increased by increasing the distance of the stimulated object from the laser head beyond the focusing point. Because the energy of the stimulus pulse remains constant, an increase in the stimulus area causes a decrease in the stimulus energy per surface area. To control the distance between the laser head and the skin, an adjustable rod was attached to the laser head. The rod was placed in contact with the skin so that the distance between the skin and the laser head, and consequently the stimulus area, could be varied. The size of the stimulus beam was measured by burning a spot on a wooden tongue depressor which was set at the distance indicated by the rod. The spot produced by the laser was toroidal, reflecting an inverse gaussian distribution of energy across the beam. The laser device had a built-in calibration system to measure the peak power of the laser pulse in watts.

Psychometric function curves were used to determine sensory thresholds. Single stimulus pulses were presented in random order at 4–6 different intensities. Each intensity was presented 10 times (except when testing effect of adapting skin temperature: 5 times). The intensity levels were selected so that they were near the thresholds determined by preliminary testing using an ascending series of stimuli. The stimuli were presented at about 10 sec intervals and were applied to 6 different spots in consecutive order to avoid possible sensitization of any one skin spot. An auditory click indicated the stimulus presentation. The subject was requested to report after hearing the click the quality of sensation, if any, by using a list of words (nothing, something, touch, warm, hot, burning, pricking, painful). The subjects were informed that hot in this experiment was considered a nociceptive sensation, in contrast to non-nociceptive warm sensation. Psychometric function curves (see Fig. 1) were constructed by plotting the percentage of responses (all sensations, or only painful sensations) from all the stimulus deliveries at each intensity of stimulation. The detection threshold, read from the psychometric function curve, was arbitrarily defined as the stimulus intensity at which the subject reported any sensation to 50% of stimulus deliveries. The pain threshold was defined as the stimulus intensity at

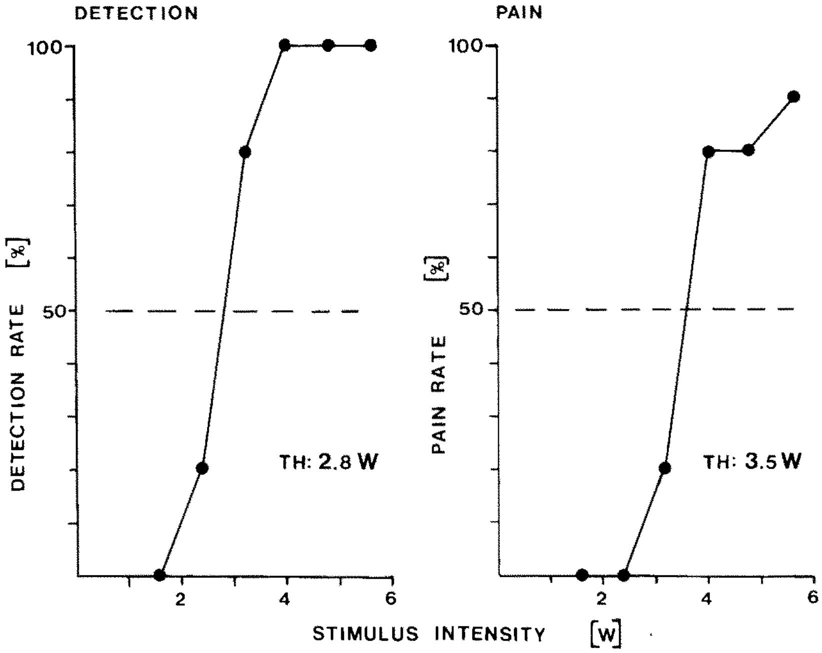

Fig. 1. Psychometric function curves relating the percentage of detected or painful responses (left and right graph, respectively) of 1 subject to the intensity of the laser stimulus applied to the hairy skin in control conditions. Each point was based on 10 deliveries of the test stimulus. Detection and pain thresholds were taken as the test stimulus intensity at which the 50% detection or pain level was reached, respectively (horizontal interrupted lines). The detection and pain threshold are also given in W in lower right corner of each group. The stimulus beam area was 64 mm^2 and the stimulus pulse duration 45 msec.

which the subject reported a painful sensation (hot, burning, pricking, painful) to 50% of stimulus deliveries. The subjects were adapted to the room temperature (23.0 + / − 0.5 °C) for at least 1 h before the experiments.

The effect of the skin region (hairy skin of the forearm and glabrous skin of the hypothenar) and size of stimulus area were tested first. Three different stimulus beam sizes were used (12.6, 19.6, and 64 mm^2). In these tests the duration of the stimulus pulse was at 45 msec. Each stimulus surface area in each skin region was tested on a separate day. The order of testing glabrous or hairy skin and 3 different sizes of the stimulus beam were counterbalanced over the subjects. Effect of stimulus pulse duration was tested later in the hairy skin of the forearm only. Three different durations of the stimulus pulse were tested (15, 30, and 45 msec), and each test was made on a separate day. Effect of adapting skin temperature was tested 3–6 months after the above mentioned experiments; only the hairy skin of the forearm was tested. The adapting skin temperature was measured by a thermocouple (iron-constantan) glued to the forearm near the stimulation site. Three different adapting skin temperatures were used (cool, control, and warm). Control was the adapting skin temperature in the room temperature which was thermostatically controlled (23.0 + / − 0.5 °C). The adaptation of the forearm skin to cool was obtained by putting the whole forearm down to the mid upper arm level in a freezer. By varying the depth of the forearm in the freezer the cooling of the forearm could be controlled with an accuracy of 1–2 °C. The adaptation of the forearm to warmth was obtained by applying an infrared light to the forearm. By varying the distance of the infrared light source from the forearm, warming could be controlled with an accuracy of 1–2 °C. The testing did not begin until the adapting skin temperature had been in the required range (control, or about 4 °C higher or lower than the control) for at least 2 min. The adapting skin temperature was continuously monitored during the experiment and required adjustments were made during the testing. When testing the effect of adapting skin temperature, the order of testing was: control, cool, control, warm and control for 3 subjects, and vice versa for the other 3 subjects: this experiment was done during 1 day for each subject.

In the reaction time study, the task of the subject was to press a button as soon as he could after experiencing a laser-evoked sensation. The stimuli were applied to 2 different places: proximal part of the hairy skin of the forearm near the elbow, and the dorsal hairy skin of the hand. The intensity of the stimulus was adjusted to a clearly painful range. The experimenter triggered the laser pulses at varying intervals ranging from 5 to 10 sec. The number of stimulus presentations in each condition varied from 20 to 30. The reaction time was measured by a computer. To avoid any possible auditory cues connected with the stimulus in the reaction time study, the subjects had headphones through which masking noise was played from a tape recorder. The subject could not see the experimenter who triggered the stimuli. The distance between the proximal and distal stimulation site in the forearm and the difference in the reaction times to stimuli applied to these two places would give the conduction velocity of the primary afferent fibers mediating the laser-evoked sensations in the hairy skin.

For statistical comparisons a least-squares linear regression analysis was made to obtain the slope and intercept values for the individual data points on the effect of stimulus pulse duration, stimulus surface area, and adapting temperature. The slope and intercept values in each condition could then be compared with those obtained in another condition using *t* test. The level $P < 0.05$ was considered a significant difference.

Results

All the subjects described non-painful sensations (warm, touch, something) at low intensities, and painful sensations at higher intensities. The stimulus intensities used in this study did not produce any skin damage in any of the subjects.

In the glabrous skin of the hand both the detection and the pain thresholds were higher than the corresponding thresholds in the hairy skin of the forearm (Fig. 2). The pain threshold for the hairy skin was almost identical with the detection threshold for the glabrous skin. The difference between the pain and detection thresholds was also larger in the glabrous skin.

The energy per surface area needed to produce any sensation (detection) or pain decreased with increasing stimulus surface area in both skin regions (Fig. 2), and this relationship was not significantly different between skin areas. However, within the hairy skin the pain threshold–stimulus area curve was significantly steeper than the curve

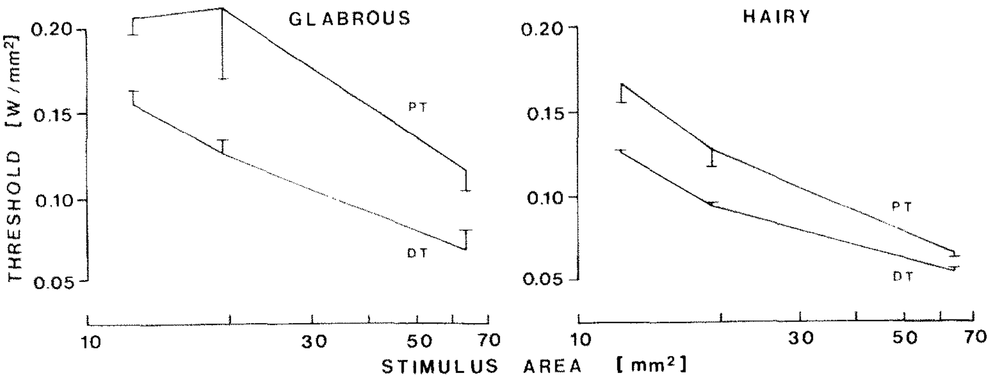

Fig. 2. Detection (DT) and pain (PT) thresholds as a function of stimulus area in hairy and glabrous skin over all subjects. The thresholds are given in energy per mm^2 needed to elicit a liminal sensation (DT) or pain sensation (PT). The vertical bars represent +/− S.E.M. (N = 6). Stimulus pulse duration: 45 msec.

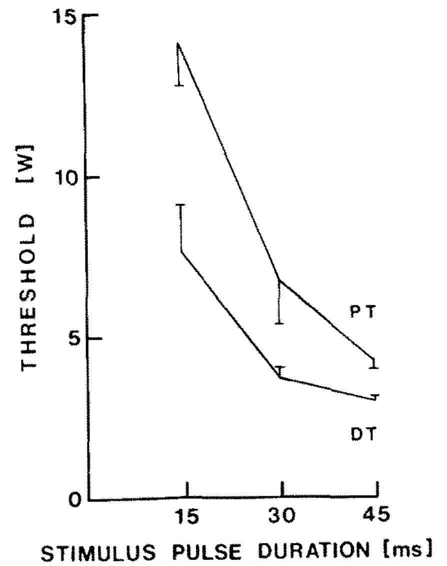

Fig. 3. Detection (DT) and pain (PT) thresholds over all subjects as a function of stimulus pulse duration. The stimuli were applied to the hairy skin, and the stimulus beam area was 64 mm^2. The vertical bars represent +/− S.E.M. (N = 6).

for the detection threshold; within the glabrous skin no such difference existed.

The variability in threshold values within subjects and across subjects, as indicated by the error bars in Fig. 2, was larger in the glabrous skin than in the hairy skin. The smallest variability values were seen with the largest stimulus surface area in the hairy skin.

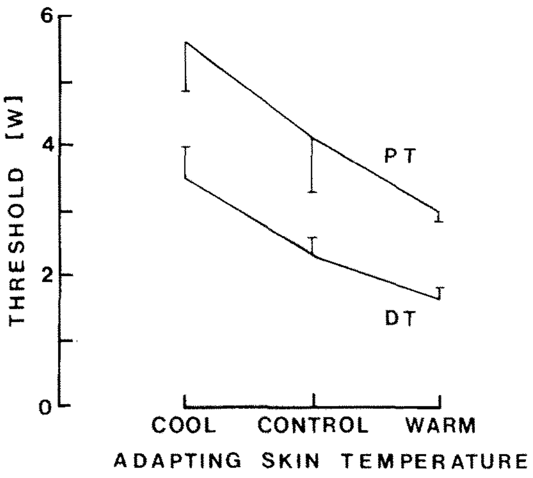

Fig. 4. Detection (DT) and pain (PT) thresholds over all subjects as a function of adapting skin temperature. The stimuli were applied to the hairy skin, the stimulus beam area was 64 mm^2, and the stimulus pulse duration was 45 msec.

Both the pain and detection thresholds were significantly elevated with decreasing duration of the stimulus pulse (Fig. 3). This effect was significantly stronger ($P < 0.05$) for the pain threshold. In addition the variability in threshold values increased in both absolute and in percentage values (standard deviation/threshold) with decreasing duration of the stimulus pulse (Fig. 3).

The adapting skin temperature in cool, control and warm conditions were 27.1 +/− 0.6, 31.5

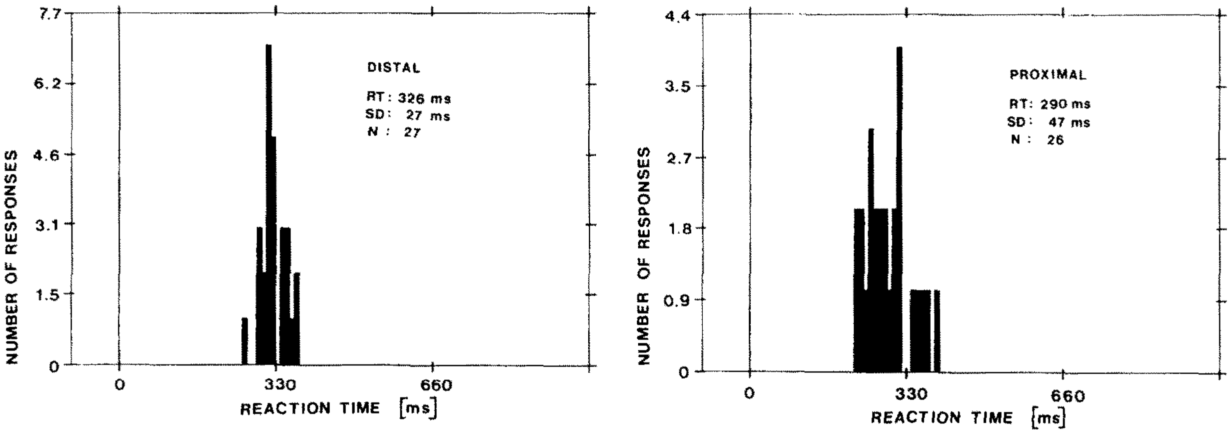

Fig. 5. Reaction time distribution histograms of 1 subject to painful laser pulse stimuli applied to the distal (left graph) or proximal (right graph) part of the hairy forearm. The mean reaction time is given in each graph. The distance between the 2 stimulation sites was 20 cm. The conduction velocity for the first laser evoked sensation in this subject was 5.6 m/sec.

+/− 0.6, and 35.3 +/− 0.3°C respectively (+/− S.E.M.; N = 6). As adapting skin temperature increased, less energy was needed to produce any sensation (detection) or a pain sensation (Fig. 4). The effect of adapting skin temperature was of equal magnitude on both detection and pain thresholds ($P > 0.05$).

In repeated threshold determinations using the same stimulus parameters (hairy skin, stimulus duration: 45 msec, stimulus area: 64 mm^2) in the same subjects, identical results were obtained even when the interval between the measurements was from 3 to 6 months (Figs. 3 and 4).

In the reaction time study, 2 of the subjects had so great a variation in reaction times (e.g., from 300 to 1500 msec within a session) that they had to be excluded from the data analysis. Thus, reaction time results are based on data obtained from 4 subjects. Fig. 5 shows an example of reaction time distributions for 1 subject. The average reaction time to laser pulse stimuli applied to the dorsal part of the hand was 461 +/− 77 msec (+/− S.E.M.; N = 4). The reaction times to laser pulses applied to the proximal part of the arm were on the average 25 msec shorter. The difference between the 2 tested skin sites varied from 20 to 25 cm. The calculated primary afferent fiber conduction velocity for the first sensation produced by the laser pulse varied from 5.6 to 10.0 m/sec.

Discussion

The results of this study support the earlier findings that short CO_2 laser pulses provide a controlled method to produce cutaneous pain in man. However, at low stimulus intensities the first sensation is non-painful [6]. Thus, from the psychophysical point of view, cutaneous stimulation with short laser pulses is not a pure pain stimulus, although at higher intensities the predominant sensation is pain. The good reproducibility of the results after an interval of several months indicates that this method gives stable threshold values when experimental conditions are adequately controlled. The longest duration of the stimulus pulse used (45 msec), the largest stimulus area (64 mm^2) and testing of the hairy skin gave the least variable results. The use of these stimulus parameters in the hairy skin also increases the probability that the sensation, if any, elicited by CO_2 laser pulses is a painful one, since with these stimulus parameters in the hairy skin the interval between the detection and pain threshold was smallest.

Pain and detection thresholds were higher in the glabrous skin of the hand than in the hairy skin of the forearm. This finding is in line with a recent study showing that the threshold for pain elicited with short CO_2 laser pulses varies regionally being highest in the glabrous skin [8]. The current study shows that the interval between the detection and pain threshold also is largest in the glabrous skin. Concerning mechanical stimulation, it is well known that tactile thresholds are lowest in the glabrous skin [36]; this fact together with the finding that the threshold for mechanically evoked pain is highest in the glabrous skin [8] indicates that for mechanically evoked sensations the interval between non-painful detection and pain is also largest in the glabrous skin. A previous study with a contact thermostimulator also shows that the difference from the non-painful warm threshold to heat pain threshold is largest in the glabrous skin [29]. These findings suggest that the glabrous skin of the hand has the widest range to sense skin stimuli below noxious intensities. Whether the neurophysiological basis for this difference between hairy and glabrous skin is due to central or peripheral factors is not known.

With increasing size of the stimulus beam the energy per surface area needed to produce any sensation or a liminal pain sensation was decreased in both the hairy and glabrous skin, and the effect was of equal magnitude in both skin areas. This finding indicates that detection and pain thresholds are not determined solely by the liminal primary afferent discharge; rather, central (spatial) summation of primary afferent impulses is important for liminal non-painful and painful sensations. Previous studies with contact thermostimulators have also demonstrated a decrease of heat pain threshold with increasing stimulus surface indicating a spatial summation effect [2,20,23,26], although in an earlier study with a conventional radiant heat stimulator the stimulus surface had little if any effect [13]. It is significant that spatial summation of laser-evoked sensations was not significantly different in the glabrous skin of the hand and the hairy skin of the forearm because in the tactile sense central summation apparently is greater in skin areas with a low cortical magnification factor (e.g., hairy skin of the arm [16,33]). However although cortical cells receive nociceptive input [22,24] nothing is known about their cortical somatotopic organization. Previous neurophysiological studies have shown that nociceptive and tactile neurons in the central nervous system do have larger receptive fields than the primary afferent fibers, indicating a convergence of afferent information, which could be the underlying neurophysiological circuitry for the spatial summation seen in the present study [37].

With decreasing stimulus pulse duration, the detection and pain thresholds were elevated. This result is expected because stimulus duration and intensity are both critical determinants of receptor activation. However, the effect of duration was significantly stronger on the pain threshold. One possible explanation of this finding would be the dependence of pain threshold by temporal summation within the central nervous system, but peripheral factors cannot be excluded. The importance of temporal summation in pain sensation has been demonstrated with electrically evoked sensory thresholds in the tooth pulp [35].

With increasing adapting skin temperature, the radiant energy needed to produce a liminal non-painful or painful sensation decreased. This psychophysical result is obtained with a radiant heat stimulator or CO_2 laser because the adapting skin temperature and the skin temperature produced by the stimulus add linearly to reach the temperature required for receptor activation. Thus, less radiant energy is required at higher adapting skin temperatures to reach the critical threshold temperature [3,14,17]. Both neurophysiological and psychophysical studies show, however, that the temperature (in °C) at which heat pain nociceptors are activated is not influenced by a change in the adapting skin temperature from 33 to 37°C [9,10,23]. In contrast, the critical temperature for the liminal warmth or cool sensation [18,19,23,25,27,31], and the corresponding discharge properties of specific warm or cool sensitive primary afferent fibers [12,18,21,32] are markedly influenced by even small changes in the adapting skin temperature. Thus, our finding that both detection and pain thresholds were equally influenced by the adapting skin temperature argues strongly against the possibility that the laser-evoked detection threshold is mediated by the activation of specific warm or cool sensitive fibers and the pain threshold by the activation of specific nociceptive C-polymodal fibers. These findings suggest, in line with a proposal made previously [6] that both the detection and pain thresholds are based on the activation of the same primary afferent fiber population, the most probable candidate for which is a slowly conducting nociceptive one [1,15,34]. This suggestion is also supported by results of our reaction time experiments, and the earlier electrophysiological finding demonstrating that specific nociceptive fibers, but not mechanoreceptive fibers, are activated by short CO_2 laser pulses [4,11].

Our findings challenge the concept that the only sensation produced by the activation of nociceptive afferents is pain. Rather, the evidence favors the conclusion that the sensation of pain is due to the central summation of inputs from nociceptive fibers that can also mediate non-painful sensations. The results of a recent study on electrically evoked prepain and pain sensation in the tooth pulp are in line with this conclusion [35] because both the prepain and pain sensation could be explained by the activation of the same fiber population.

The results of this study indicate that short CO_2 laser pulses provide a useful method in pain research. This stimulus methodology seems to produce a rather selective activation of nociceptive fibers, eliciting painful and non-painful sensations.

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