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Relationships between the intensity and duration of Peltier heat stimulation and pain magnitude

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Abstract

Ramp-and-hold heat stimulation with a Peltier thermode is a standard procedure for quantitative sensory testing of human pain sensitivity. Because myelinated and unmyelinated nociceptive afferents respond preferentially to changing and steady temperatures, respectively, ramp-and-hold heat stimulation could assess processing of input from A-delta nociceptors early and C nociceptors late during prolonged thermal stimulation.

In order to evaluate the progression from dynamic change to a steady temperature during prolonged Peltier stimulation, recordings of temperatures at the probe-skin interface were obtained. First, recordings of temperature during contact-and-hold stimulation (solenoid powered delivery of a preheated thermode to the skin) provided an evaluation of heat dissipation from the beginning of stimulation, uncontaminated by ramping. The heat sink effect lasted up to 8 sec. and accounted in part for substantial increases in pain intensity as a combined function of durations from 1–16 sec. and stimulus intensities from 43°C to 59°. Recordings during longer periods of stimulation showed that Peltier stimulation generated feedback oscillations in temperature for up to 75 sec that were tracked by subjects' continuous ratings of pain. During 120 sec. trials, sensitization of pain was observed over 45 seconds after the oscillations subsided. In contrast, sensitization was not observed during 130.5 sec. of stimulation with alternately increasing and decreasing temperatures that maintained a target eVAS rating of 35. Thus, long duration stimulation can be utilized to evaluate sensitization, presumably of C nociception, when not disrupted by oscillations inherent to feedback control of Peltier stimulation.

Keywords

Pain sensitization; pain modulation; pain psychophysics; thermal sensitivity; pain sensitivity

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DISCLOSURES

A.P. Mauderli is the CEO of Neuroanalytics Corp., Gainesville, FL. Neuroanalytics is constructing an improved version of the psychophysical test system for commercial sale. Dr. Vierck is a member of the board of directors of Neuroanalytics.

AUTHOR CONTRIBUTIONS

C.J. Vierck contributed to design of the experiments, analyzed the data and wrote the first draft of the paper. A.P. Mauderli designed and built the psychophysical test system, contributed to design of the experiments and proofed the manuscript. J.L. Riley contributed to design of the experiments, supervised all the data collection in his laboratory and proofed the manuscript.

INTRODUCTION

Evidence indicates that A-delta nociceptors respond to abrupt or changing levels of stimulation, including heat (4; 10; 23; 25), providing fast onset, first pain sensations that elicit reflex adjustments and also inform a subject about new levels of pain with constantly updated information on its intensity. C nociceptors respond with long latencies (second pain) and low levels of discharge during slowly increasing or maintained stimulation, providing information on tonic pain intensity (1; 16; 23–25). An important feature of C nociception is exemplified by NMDA sensitive temporal summation (windup), which amplifies second pain in response to repetitive activation of C nociceptors at frequencies of 0.3 Hz or greater (14; 18). This form of central sensitization is highly relevant to chronic pain involving tissue injury with inflammation that activates C nociceptors.

Typically, experimental investigations of thermal pain ask subjects to rate sensation intensities following presentation of short duration stimuli that activate myelinated (A-delta) and possibly unmyelinated (C) nociceptors. In attempts to separately evaluate C nociception with paradigms intended to produce windup, repetitive up and down ramps have been utilized. However, ramping stimulation activates A-delta nociceptors (8; 18). Also the windup procedure is cumbersome, particularly for relating the threshold for or rate of sensitization to stimulus intensity. Thus, it would be advantageous experimentally to present long duration thermal stimuli that preferentially activate A-delta nociceptors during and shortly after onset (e.g., during ramping) and then selectively activate C nociceptors with maintenance of stimulation until A-delta nociceptors adapt and cease firing. For evaluation of C nociception, it is important to minimize A-delta activation, which can summate with (8) or inhibit input from C nociceptors (2; 6–8; 17; 22).

Ramp-and-hold stimulation with a Peltier thermode is the most common method for delivering nociceptive heat to the skin. Advantages are considered to be that the baseline temperature can be controlled by ramping from and returning to a non-nociceptive temperature (e.g., 33°C) from trial to trial, and tactile stimulation of A-beta afferents at the beginning of a trial is prevented. Commercially available Peltier devices have maximized ramp rate, possibly to mimic natural thermal stimulation (e.g., when a hot object contacts the skin and the rate of heat transfer is high) and because brief stimuli permit efficient presentation of multiple trials with minimal trauma to the skin. Efforts to demonstrate the effect of ramp rate on sensation intensity have been indeterminate, finding no effect or opposite effects on threshold and suprathreshold pain, depending on the ramp rate and the duration of stimulation (9; 11; 12).

Ramp-and-hold Peltier stimulation is not a straightforward matter of ascending directly to a target temperature and then holding that temperature steadily. An inherent property of feedback control over Peltier devices in systems optimized for fast ramp speed is that the target temperature will be overshoot, and the maximum temperature and rating of initial stimulation will be underestimated. Subsequent to the initial ramp, the target temperature will be undershot and overshoot cyclically, and it is important to measure the amplitude and duration of these variations. Otherwise, changes over time, such as a reduction in sensation intensity, can be regarded as adaptation (3; 5) when the subjects are responding to temperature reductions. Previous investigations often have relied upon manufacturers' specifications or on a possibly filtered output from thermal transducers within the device. Alternatively, performance of the stimulator can be assessed by measurements of temperature at the probe-skin interface (13). Relationships between Peltier activation, skin temperature and sensation intensity depend on properties that vary between thermodes (e.g., the settings for feedback control and the power of the device) and properties of skin that differ between sites.

In attempts to define long-term relationships between thermode temperatures at the probe-skin interface and psychophysical ratings of pain, 5 experiments were conducted. The amount and time-course of heat transfer (the heat-sink effect) when the probe was in contact with the skin was estimated by measuring temperatures at the probe-skin interface during contact of a preheated probe with the skin (contact-and-hold stimulation) (experiment 1). Stimulus-response functions for durations of contact-and-hold stimulation up to 16 sec. (experiment 2) and a comparison of contact-and-hold and ramp-and-hold stimulation over 19–23 sec. (experiment 3) revealed the progression of pain magnitude in relation to the heat-sink effect and influences of oscillations in the probe-skin temperature as a result of Peltier feedback control. Prolonged stimulation (120 sec.) verified the need to outlast oscillations in probe temperature in order to observe the effect of long-term, unvarying nociceptive stimulation (experiments 4 and 5). Implications of relationships between tonic unvarying pain and the intensity of clinical pain are discussed.

MATERIALS AND METHODS

Subjects

Potential subjects underwent a preliminary screening visit to ensure that they met inclusion criteria requiring no significant spontaneous pain anywhere in the body, no ongoing pharmacotherapy with narcotics or antidepressants, and no disease that might affect pain perception (e.g., neurological disorders, psychiatric disorders, diabetes, hypertension, serious cardiovascular disorders or chronic pain diseases such as fibromyalgia syndrome). Informed consent was obtained from all subjects. This investigation was approved by the Institutional review board of the University of Florida College of Medicine.

Peltier thermoelectric device

The stimulator system used in these experiments was designed and built by one of the investigators (A.P.M.). The thermode is heated and cooled by a solid-state heat pump (Peltier device). The Peltier device is sandwiched between a 26 × 26 mm flat copper thermode and a heat reservoir made of an aluminum block. The temperature of the heat reservoir is controlled by internal water circulation. In heating mode, the Peltier device pumps heat from the reservoir to the thermode. In cooling mode (e.g., when returning to baseline) heat is pumped from the thermode to the reservoir. For temperature control, the sampling rate is 10 samples/sec. The Peltier device delivers 100% of its power initially when ramping toward a setpoint temperature. When the temperature nears the setpoint (within a proportional band) the power decreases proportionally as the difference between the actual and set temperatures becomes smaller. In addition, the temperature controller uses an integral parameter to eliminate temperature droop. Control parameters and heat reservoir temperatures are set to achieve an acceptable compromise between a fast ramp speed and minimal oscillations during setpoint changes. Using a Peltier device, it is impossible to produce sharp pulse-like temperature transitions that precisely match and hold a new setpoint, and transient temperature changes cannot be avoided when the thermal load changes. Thus, it is imperative to record unfiltered thermode temperatures as part of a data set.

Measurement of temperature at the probe-skin interface

Thermode temperature is sensed by a thermistor that is embedded in a recess in the center of the copper thermode, 0.3 mm from the surface that contacts the skin. With this placement, the thermistor reports the temperature of the copper plate in contact with the skin, and it is sensitive to heat loss from the probe to the skin. The temperatures at the probe-skin interface during Peltier stimulation are dependent upon a number of features of an experimental setup: 1) the power of the system in caloric output per time, 2) thermal load (temperature of the

skin, firmness of skin-thermode contact, hairy or glabrous skin), 3) the temperature range the system is operated in, 4) the temperature gradient between the thermode and the reservoir of circulating water, and 5) control parameters for the Peltier device (the proportional band and integral and derivative settings). The net effect of these factors is assessed by measurement of temperatures at the probe-skin interface.

Psychophysical testing

Thermal stimuli were administered with a 26×26 mm thermode which was electronically held at the desired temperature by a Peltier thermoelectric device. It was brought from off the skin onto light contact with the thenar eminence of either hand by solenoid activation. In some testing sessions, the thermode was preheated to a nociceptive temperature before contacting the skin for predetermined durations (contact-and-hold stimulation). In other sessions, the thermode was maintained at 33°C for initial skin contact, and nociceptive stimulation was delivered 12 sec. later by ramping to and holding a target temperature for predetermined durations (ramp-and-hold stimulation). The subjects were asked to rate pain intensity by moving the slider of an electronic visual analog scale (eVAS) from left to right. Use of the scale and its end-points (“no pain” on the left and “intolerably intense pain” on the right) were explained by a standardized video. The slider’s position was recorded as a percentage of its total travel (0–100). The slider was mounted into the surface of a small inclined desk, which was positioned to facilitate precise operation with the non-stimulated hand. During the experiment, the subject was separated from the investigator by an equipment rack to eliminate non-verbal communication and transmission of bias. Before some testing sessions (experiments 3–5), the subjects were instructed to rate moment-to-moment levels of pain throughout a period of stimulation (trial). Slider position was sampled by software at regular intervals (1.0 or 1.5 sec.) during stimulation. In experiment 2, the subjects moved the slider to a position which represented the maximum level of pain during the most recent period of stimulation. The slider position was sampled at the end of a 5 sec. interval after stimulus termination, and the slider was automatically returned to the start position before the next period of stimulation (trial).

Experiment 1: Measurement of the heat sink reaction of skin during contact-and-hold stimulation

Three subjects (2 females, 1 male; ages 23, 51 and 70) received 6 trials of contact-and-hold stimulation in one daily session. The order of stimulus intensities across trials was 43°C, 45°C, 47°C, 49°C, 51°C and 53°C, with an ITI of 3 min. The purpose of these trials was to track changes in probe temperature in response to the heat-sink effect of skin contact. Accordingly, trial durations were determined by the time required for the probe temperature to return to the set temperature following skin contact. Probe temperature was sampled at 1 sec intervals.

Experiment 2: Pain sensitivity as a function of thermal stimulus duration

Ten subjects (7 males, 3 females; ages 20 – 65) received individual trials of contact-and-hold stimulation of the thenar eminence for different durations of stimulation at temperatures established before skin contact. Two sessions per day involved ascending series of stimulus intensities, starting at 43°C, incrementing by 1°C from trial to trial, and ending when the eVAS rating on a trial was 65. The intertrial interval (ITI) was 30 sec. The order of sessions involving left and right hand stimulation was varied randomly within days. The intersession interval (ISI) was 30 min. Each session presented one stimulus duration. A total of 6 sessions per subject provided stimulus-response functions for durations of 1, 2, 3, 4, 8 and 16 sec. The interval between days of testing for individual subjects was 2 days. The order of stimulus durations between sessions and days was randomized between subjects.

Experiment 3: Comparison of the time-course of eVAS ratings during contact-and-hold and ramp-and-hold stimulation

Twelve subjects (7 males, 5 females; ages 20–59) received a training session to orient them to continuous rating of thermal pain and to determine a temperature that would elicit moderate pain. The training session consisted of 30 sec trials of contact-and-hold stimulation of the thenar eminence. The ITI was 30 sec., and the thermode temperature was increased from 44°C, in 1°C steps until an eVAS rating of 40 was achieved. Subjects that did not reach the target rating of 40 were assigned 49°C. On subsequent days, single trials of ramp-and-hold stimulation and contact-and-hold stimulation, with an ITI of 30 min, were presented within each of 2 testing sessions, using the target temperature established during the training session. The order of left and right thenar stimulation and of contact-and-hold and ramp-and-hold trials was varied randomly within and between subjects. Contact-and-hold trial durations were 19 sec. Ramp-and-hold trials consisted of 12 sec of pre-trial contact with the thermode temperature set at 33°C, followed by ramp-and-hold to each subject's target temperature for 23 sec. Thermode temperatures and eVAS ratings were sampled at 1 sec intervals. The subjects were instructed to rate sensation intensity continuously during thermal stimulation.

Experiment 4: Ramp-and-hold thermal stimulation for 120 sec

Thirty two subjects (17 males, 15 females; ages 18–75) received a training session, as described above, to determine a temperature that would elicit moderate pain during 30 sec. of ramp-and-hold stimulation of the thenar eminence. On 1 or 2 subsequent days, 120 sec of ramp-and-hold stimulation of the non-dominant thenar eminence at the predetermined temperature was rated continuously, with sampling of thermode temperatures and eVAS ratings at 1.0 sec intervals. Fifteen subjects were tested on 2 separate days, for a total of 47 sessions among the 32 subjects.

For comparison with measurement of temperatures at the thermode-skin interface, the Peltier device was activated for 120 sec. of ramp-and-hold stimulation to target temperatures of 45°C to 53°C in 1 deg. increments, and probe temperatures were recorded in the absence of skin contact.

Experiment 5: Long-term stimulation at temperatures that maintain target eVAS ratings

Experiment 4 was designed to reveal sensitization or desensitization of pain by increased or decreased eVAS ratings during long-term thermal stimulation at a single target temperature. Experiment 5 was designed to reveal sensitization or desensitization if the average temperature increased or decreased during sessions in which the subjects tracked a target eVAS rating. For a thorough description of this paradigm, see (21). Ten subjects (5 males, 5 females; ages 20 – 32) were tested on 3 separate days with a paradigm that adjusted stimulus intensity up or down to maintain an eVAS rating of 20 for a duration of 150 sec., followed by maintenance of eVAS 35 for 130.5 sec. Stimulation was continuous but was ramped up, at 1.5 sec intervals, from 43°C until the target eVAS 20 rating was exceeded; then the temperature was decreased until a rating <20 occurred; subsequent increases and decreases in temperature tracked eVAS 20 and then eVAS 35. Temperatures were ramped up or down by 0.1°C to 0.3°C increments on the basis of differences in eVAS ratings from the target. Temperatures and eVAS ratings were sampled 0.1 sec. before each temperature adjustment.

Data analysis and statistical comparisons

Statistical tests for experiment 2 were conducted with GraphPad Instat 3 (La Jolla, Ca). Differences in temperatures producing eVAS ratings equal to or greater than 10 or 40 were compared for successive stimulus durations (1s vs. 2s, 2s vs. 3s, etc.) with t tests for

dependent measures. Differences in eVAS units/°C, as a measure of amplification by stimulus duration, were tested with ANOVA for repeated measures.

RESULTS

Experiment 1: Measurement of the heat sink reaction of skin during contact-and-hold stimulation

For contact-and-hold stimulation, the target temperature is present at the probe-skin interface from the beginning of a trial, in contrast to the more common technique of ramping up to a target from a non-nociceptive resting temperature. With immediate presentation of the target temperature, heat dissipation from the probe through the skin can be observed by recording temperatures at the probe-skin interface during stimulation. Figure 1 shows the heat-sink effect for contact-and-hold stimulation of the thenar eminence when the probe was preheated to temperatures of 43°C, 45°C, 47°C, 49°C, 51°C or 53°C. The curves are normalized to show changes in probe temperature over time relative to the set temperature. The magnitude of the heat sink effect was proportionate to the set temperature, but the time-course of change was the same for each temperature. Thus, according to measurements of temperature at the probe-skin interface during contact-and-hold stimulation, regardless of the set temperature, 8 seconds was required for the Peltier probe to re-establish the set temperature.

Experiment 2: Pain sensitivity as a function of thermal stimulus duration

Figure 2A shows stimulus-response functions (temperature-eVAS functions) for contact-and-hold durations of 1, 2, 3, 4, 8 and 16 seconds. The stimulus-response functions for pain increased greatly in magnitude with the duration of heat stimulation, including 16 sec., which exceeded the heat sink duration as measured by probe temperature. Figure 2B demonstrates this for near threshold, very mild pain (eVAS 10) and for a moderate level of pain (eVAS 40). For brief (1 sec.) stimulation, high temperatures (51.6°C and 57.6°C) were required to elicit mild or moderate pain, respectively, compared to temperatures of prolonged stimulation (16 sec.) that elicited mild and moderate pain at 46.1°C and 47.8°C. The differences in temperature as a function of duration were more pronounced for moderate pain than for mild pain, as revealed by statistical comparisons of temperatures during adjacent stimulus durations (1 vs. 2 sec, 2 vs. 3 sec., etc.) that were required to elicit eVAS 40 and eVAS 10 (Table 1). These comparisons were highly significant for all the eVAS 40 comparisons but only differed for eVAS 10 when comparing 2 vs. 3 seconds of stimulation. Another demonstration of increased sensitivity with heat duration is shown by a plot of the average increase in eVAS units per degree increase in temperature (Figure 3). The magnification factor for ratings of a 16 sec. stimulus was more than 10 fold higher than for ratings of a 1 sec. stimulus. The difference in sensitivity across durations 1–16 sec. was highly significant ($F=32.24$, $df=5$, $p<0.0001$).

Experiment 3: Comparison of the time-course of eVAS ratings during contact-and-hold and ramp-and-hold stimulation

Figure 4A shows the dynamics of temperature and eVAS ratings over time during contact-and-hold stimulation of 12 subjects with an average set temperature of 48.2°C. For these subjects, the probe temperature declined to 47.7°C at 3 sec., returned to the set value at approximately 7 seconds following contact (revealing the heat-sink effect) and overshot the set temperature to peak at 48.5°C and 9 sec. Typical of the sensitizing trends that increase ratings beyond the peak of an ascending temperature progression (19), the peak eVAS rating occurred at 12 sec. The oscillations in feedback control continued as the probe temperature decreased to 48.1°C at 14 sec., followed by a desensitizing trend in eVAS ratings to a low value at 17 sec. This progression of temperatures illustrates oscillations from feedback

control of the probe which largely determined eVAS ratings during the “hold” period following contact. The high peak and low peak eVAS ratings (41.9 and 35.1) in response to preceding high and low peaks in probe temperature (48.5°C and 48.1°C), amounted to a sensitivity of 10.8 eVAS units per degree centigrade.

Figure 4B shows the dynamics of temperature and eVAS ratings over time during ramp-and-hold stimulation of the 12 subjects. Following an initial ramp from 33°C to 46.87°C in 2 sec. (ramp rate of 6.9°/s), the probe temperature more slowly approached the target to minimize overshooting. The slow portion of the ramp (0.12°/s) in the proportional band overshoot the target to a maximum of 48.49°C at 16 sec. Following the peak in thermode temperature, eVAS ratings reached a delayed maximum of 47.75 at 18 sec., then declined to 35.04 at 23 sec. when the probe temperature was 48.1°C.

Direct comparison of contact-and-hold and ramp-and-hold trials delivered to the same subjects at the same temperatures revealed the importance of relating temperatures at the probe-skin interface to continuous pain ratings. For trials of 1–11 sec., eVAS ratings for tap-and-hold would have exceeded ratings for ramp-and-hold, but the reverse would have been the case if trials of 12–18 sec. had been presented. Pain ratings at any time for the two methods of skin heating were determined by temperature and time, as determined by oscillations around the target temperature, not by the initial rate of ascent to that temperature (ramp rate). These relationships are detailed in Table 2: (A) At 2 sec., the end of the initial fast ramp (ramp 1), the contact-and-hold rating was higher than the ramp-and-hold rating, as was the temperature; (B) at the end of the secondary ramp to 48.5°C, the rating for ramp-and-hold stimulation was greater at 15 sec than the rating for the same peak temperature of contact-and-hold stimulation at 8 sec.; (C) at 48.1°C, the low point of the undershoot ramp (ramp 3) for both methods of stimulation, the ratings were similar for contact-and-hold (39.3) at 13 sec. and ramp-and-hold (39.1) at 21 sec. Thus, at different points for these forms of stimulation, the eVAS ratings were determined by (A) temperature, (B) time or (C) recent history (oscillation).

Experiment 4: Ramp-and-hold thermal stimulation for 120 sec

Experiment 3 indicated that long trial durations would be required to appreciate whether oscillations in probe temperature and their effects on pain ratings would diminish over time. Accordingly, 32 subjects continuously rated pain intensity during ramp-and-hold heat stimulation of the thenar eminence for 2 min., with sampling at 1 sec. intervals. Figure 5A documents oscillations in probe temperature for up to 70 sec. of stimulation. The oscillations occurred reliably for the group of subjects with an average period of 13.6 sec following the initial peak temperature (at 15 sec.). For the first 75 sec. of stimulation, the average eVAS rating increased in steps, approximately synced with oscillating phases of increasing probe temperatures. However, from 75 to 83 sec. the peak-to-peak oscillation in temperature diminished to 0.03°C. From 75 to 120 sec. of stimulation, when the probe temperature was nearly constant, eVAS ratings increased steadily from 28.53 to 39.68 (average temperature of 47.74°C; standard deviation of 0.01°C). Thus, sensitization occurred over the last 45 sec. of nociceptive stimulation without the influence of feedback oscillations in probe temperature.

Figure 5B directly compares the average temperatures at the probe-skin interface, as shown in Figure 5A, with temperatures recorded from the probe during 48°C ramp-and-hold stimulation in air (no skin contact) for 120 sec. Regular peak to peak oscillations of 0.2°C were observed throughout the 120 of stimulation in air. In contrast, the magnitude of positive and negative peaks around the set temperature decreased over 120 sec. of cutaneous stimulation. Contact with the skin progressively stabilized control over the probe temperature because the control parameters were optimized for a thermal load.

Experiment 5: Long-term stimulation at temperatures that maintain target eVAS ratings

Experiment 5 tests whether sensitization occurs if regular oscillations in temperature are present throughout trials of long-term heat stimulation. Ten subjects were tested on a paradigm that controls oscillations in temperature to maintain a target eVAS rating (21). Pain intensity was rated continuously as the probe temperature increased in 0.1°C to 0.3°C increments, at 1.5 sec intervals, until the target rating was equaled or exceeded; then the temperature decreased until the target rating was equaled or a lower rating occurred, etc. The top panel of Figure 6 shows the early component of the testing session, beginning with the first eVAS rating that exceeded a target of 20. Some desensitization occurred early in this component of the session; the temperatures which maintained a rating of 20 increased over the first 48 sec. of testing. Little or no sensitization or desensitization occurred during the remainder of the 147 sec. of testing with a target rating of 20. The lower panel of Figure 6 shows the second component of the testing session that continued without interruption from the first but with a target eVAS rating of 35. From the first rating above 35 until the last rating, 130.5 sec. later, there was no sensitization (no decrease in average temperature) or desensitization (increase in average temperature).

DISCUSSION

The duration of cutaneous heat stimulation powerfully influenced pain magnitude, as shown by ratings of temperatures sufficient to elicit eVAS ratings up to 65 during contact-and-hold stimuli of 1 to 16 sec. (experiment 2; Figure 1). These stimulus-response functions revealed an increase in pain sensitivity with duration that was greater than 10 fold (as expressed in eVAS units/°C). This finding conflicts with the classical concept of a single power function that fits a uniform stimulus-response relationship for thermal pain (15). Tests of multiple trial durations revealed a family of stimulus-response functions with enhanced sensitivity to prolonged stimulation. The strong interaction between temperature and duration is consistent with the role of pain in protection against noxious stimuli that threaten tissue damage by protein denaturation.

It is important to note that the eVAS ratings in experiment 2 reflected the maximum pain in response to the preceding temperature that was preset before skin contact. The ratings did not reflect either the pain level or the exact temperature at the end of the trial. In order to describe the progression of intensity with increasing thermal stimulus durations, pain was rated continuously in experiments 3 and 4, along with recording of temperature at the probe-skin interface. These tests revealed changes in ratings that were determined by temperature and time, as determined by oscillations in feedback control of the Peltier probe and the thermal transfer properties of skin. During contact-and-hold stimulation, pain ratings increased as the probe temperature recovered from an early heat-sink effect of thermal transfer through the skin. The time required to compensate for heat transfer and restore the set temperature at the probe-skin interface must contribute to the relative lack of sensitivity to short duration contact-and-hold stimulation in experiment 2. Heat transfer to receptors deep in the skin occurs gradually during the heat-sink period. Over a longer period of ramp-and-hold stimulation, equilibrium appeared to be established between the probe temperature and thermal storage within the underlying skin. This required approximately 75 sec., when feedback oscillations in probe temperature nearly ceased. At this point in time for an average target temperature of 47.7°C the probe temperature was stable when in contact with the skin, in contrast to activation of the probe in air. When oscillations by the Peltier probe ceased, it is likely that the thermal gradient within the skin and underlying tissue was stable.

The cyclical changes in probe temperature in air were small (0.2°C positive to negative peak difference) and did not differ for target temperatures of 45°C to 53°C (data not shown). Similar oscillations in temperature at the probe-skin interface occurred over 75 sec., and

these were sufficient to modulate pain ratings. During the temperature oscillations, maximum pain ratings lagged the maximum temperature and minimum pain rating lagged the minimum temperature (e.g., Figure 4A), suggestive of sensitizing and desensitizing modulation that occurs during alternating ascending and descending series of temperature progressions (19). In addition, changing levels of stimulation maintain activation of myelinated nociceptors, which is inhibitory to C nociception (1; 2; 4; 6; 7; 10; 17; 20). These conditions pose the question as to whether oscillating temperature progressions suppress an overall sensitization of C nociception that is expected to occur with maintained stimulation (7; 16). In an attempt to address this question, a method of eVAS tracking was utilized (experiment 5) (21). Probe temperature increased in small steps until the target eVAS was equaled or exceeded and then decreased until the rating was equal to or less than the target, etc. If sensitization occurred, the temperatures that maintain the target rating would progressively decrease. This method of altering temperatures in small steps likely activated myelinated and unmyelinated nociceptors. However, no sensitization was observed over several minutes of tracking eVAS 20 and then several minutes of tracking eVAS 35.

In contrast to the lack of sensitization during maintained oscillation of thermode temperatures, ramp and hold stimulation to a target temperature for 2 min. was eventually associated with considerable sensitization. Following 75 sec. of temperature oscillation by feedback control over the Peltier probe, the temperature remained relatively steady, favoring activation of C nociceptors (23; 25). Over 45 sec. of maintained stimulation free of feedback oscillations in temperature, pain sensitization was apparent.

Conclusions

The purposes of this experiment were to: 1) determine the combined effects of stimulus duration and intensity on psychophysical ratings of heat pain, and 2) relate measurements of temperature at the interface between the skin and a Peltier probe to psychophysical ratings of long duration heat stimulation. Ratings of maximal pain over durations of contact-and-hold stimulation that produced a single peak in probe temperature revealed a dramatic enhancement of pain as a function of stimulation intensity and duration. For example, 46°C did not elicit eVAS ratings above 10 for durations of 1–16 sec., but 50°C produced an average eVAS rating (across subjects) of 5.9 for a 1 sec. stimulus, 31.9 over 4 sec. and 75.3 during 16 sec. of stimulation.

Interpretation of the effects of long duration stimulation required continuous assessment of pain levels and measurement of temperature at the probe-skin interface. These measurements showed that ramping up to and holding a target temperature is influenced by heat transfer through the skin, with evidence for several phases: (A) an early loss of heat to the skin that was overcome in 6–8 sec. by feedback control over probe temperature, and (B) a prolonged period of approximately 75 sec. in which oscillations in probe temperature gradually diminished, suggesting that heat storage by the skin eventually reached equilibrium with the probe temperature. Prior to stabilization of the probe temperature, the “hold” phase of feedback-controlled Peltier stimulation included peaks and valleys in stimulus intensity that influenced pain ratings moment-to-moment. Subsequently, a constant level of nociceptive stimulation, presumed to selectively activate unmyelinated nociceptors, did not generate stable eVAS ratings. Unwavering heat stimulation was associated with sensitization, consistent with demonstrations of temporal summation (windup) of input from C nociceptors (14; 18).

An implication of these findings is that pathological C nociceptor activation without A-delta nociceptor activation is likely to summate and become progressively more intense. Additionally, these results suggest that the efficacy of counter irritation procedures such as

transcutaneous electrical nerve stimulation (TENS; (4; 6; 7; 17) might be enhanced by oscillating activation of myelinated nociceptors that invokes and refreshes modulatory influences without adaptation (10).

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HEAT SINK EFFECT

Figure 1.

Changes in temperature at the probe-skin interface during the first 9 sec. of contact-and-hold stimulation of the thenar eminence. The magnitude of the peak decrease in temperature at 3 sec. was related to the preset temperature of the probe,

Figure 2.

A. Subjects rated the maximum intensity of pain, using the 0–100 eVAS scale, during contact-and-hold stimulation. Ratings occurred within 5 sec. of the end of the previous trial. Pain intensity was strongly related to the duration and intensity of Peltier stimulation. B. Threshold values for mild (eVAS 10) and moderate (eVAS 40) pain are plotted as an inverse function of stimulus duration. The data are fitted with a 2nd order polynomial function.

Figure 3. Magnification of maximal pain during trials of Peltier thermal stimulation (eVAS units per degree C) is plotted as a function of stimulus duration. Error bars are standard errors.

Figure 4. Temperatures at the probe-skin interface (open symbols) and eVAS ratings of pain intensity (closed symbols) are shown at 1 sec. intervals during: A. contact-and-hold stimulation and B. ramp-and-hold stimulation. Temperatures on the right axis and eVAS ratings on the left axis. The average target temperature for the group of subjects is shown as a horizontal double line.

Figure 5.

A. Temperatures at the probe-skin interface (open symbols) and eVAS ratings (closed symbols) at 1 sec. intervals during 120 sec. of continuous ramp-and-hold stimulation. Temperatures on the right axis and eVAS ratings on the left axis. B. Temperatures relative to the target of ramp-and-hold activation of the Peltier probe during 120 sec. of stimulation in air (gray line) and during contact with thenar eminence skin (black line). The target temperature for stimulation of skin averaged 48.2°C, and the target for activation in air was 48°C.

Figure 6.

Temperatures at the probe-skin interface (open symbols) and eVAS ratings (closed symbols) at 1.5 sec. intervals during stimulation sequences that tracked a target eVAS rating of 20 (upper panel) and then 35 (lower panel). Desensitization (a gradual increase in temperatures) was observed over approximately the first 45 minutes of tracking eVAS 20. Subsequently, there was no net sensitization or desensitization. Linear trendlines (double lines) are fit to both sets of data.

Table 1

Statistical comparisons of minimal temperatures for eVAS ratings of 10 and 40

STIMULUS DURATION	eVAS 10				eVAS 40			
	Mean	S.E.	t	p	Mean	S.E.	t	p
1 Sec.	51.6	0.67			57.60	0.82		
2 Sec.	50.6	0.55	2.005	0.076	54.66	0.74	5.714	0.0003*
3 Sec.	48.6	0.51	3.289	0.009*	52.18	0.57	5.555	0.0004*
4 Sec.	47.6	0.55	1.635	0.136	50.90	0.37	3.916	0.004*
8 Sec.	46.8	0.42	1.758	0.113	49.36	0.32	3.713	0.005*
16 Sec.	46.2	0.46	2.012	0.075	48.06	0.23	6.047	0.0002*