RELEASE OF COLD-INDUCED BURNING PAIN BY BLOCK OF COLD-SPECIFIC AFFERENT INPUT

by DAVID YARNITSKY and JOSÉ L. OCHOA

(From the Department of Neurology, Good Samaritan Hospital and Medical Center and Oregon Health Sciences University, Portland, Oregon, USA, and Department of Neurology, Rambam Medical Center, Haifa, Israel)

SUMMARY

While the pure sensation of cold is evoked by activation of a specific set of afferent channels, an additional set is believed to be activated by noxious low-temperature stimuli evoking cold pain. At primary afferent level, the channels concerned with the cold fraction of cold pain are served by myelinated A delta cold-specific fibres, whereas those concerned with the pain fraction are served by unmyelinated C nociceptors. In the present study, interaction between the two types of afferent input underlying cold pain was investigated by selectively blocking conduction in myelinated fibres. When doing so to the point of abolishing cold sensation, ramps of low-temperature stimuli eventually evoked a first sensation of burning pain. In addition to, and contemporaneous with, this change in quality, a significant decrease in pain threshold (reduction in required stimulus energy) was recorded when applying a noxious low-temperature stimulus. Such exaggeration in magnitude of low temperature-induced pain and the unmasking of its burning quality by A fibre block imply release of central sensory transmission due to removal of inhibitory primary afferent input. Myelinated fibres transmitting either tactile, cold sensations or both could exert this inhibition. Previous evidence of suppression of pain by low-temperature stimuli indicates that it is the cold-specific input that normally exerts this central gating on nociceptor input. The present results may also offer an explanation for the occurrence of a syndrome of burning pain on cold exposure in neuropathic patients with impaired ability to perceive cold.

INTRODUCTION

Lowering skin temperature evokes a painless cold sensation which, on further reduction in temperature, becomes a cold and painful sensation: cold pain. Early thinking on sensory mechanisms interpreted pain from intense high or low temperature stimuli as simple upgrading in magnitude of warm or cold sensation due to increased afferent input (see Zotterman, 1972). Current thinking supports separate specific afferent channels as evoking thermal specific and thermal pain sensations. Indeed, there is now strong experimental and clinical support for the concepts that at primary afferent level (1) warm sensation is mediated by specific unmyelinated C fibres (Konietzny and Hensel, 1975; Hallin et al., 1982); (2) cold sensation is mediated by small myelinated A delta fibres (Darian-Smith et al., 1973; MacKenzie et al., 1975; Adriaensen et al., 1983); (3) heat-induced pain by unmyelinated polymodal nociceptors (Torebjörk, 1974; van Hees and Gybels, 1981), with participation, under certain circumstances, of small myelinated (A delta) nociceptors (LaMotte and Campbell, 1978); and (4) cold-induced pain by unmyelinated nociceptors.
polymodal nociceptors (Torebjörk, 1974). It is thought that the cold quality of the pain induced by low temperature stimuli reflects coactivation of cold-specific A delta afferents (LaMotte and Thalhammer, 1982; Saumet et al., 1985).

The advent of quantitative sensory testing techniques to measure psychophysical thresholds for warm, cold, heat pain and cold pain sensations (Fruhstorfer et al., 1976; Lindblom and Verrillo, 1979; Claus et al., 1987; Ziegler et al., 1988) offers the opportunity to examine the detailed relationship between thermal specific and thermal pain submodalities under experimental conditions of dissociated nerve block. In doing so, through local compression-ischaemia, the present study not only confirms that low temperature-induced pain persists after abolition of cold sensation, but shows that its quality and magnitude are strikingly modified. Indeed, A fibre block of cold-specific input leads to an exaggeration of low temperature-induced pain, which becomes endowed with a burning quality.

These findings are a mirror image of those reported by Bini et al. (1984) who demonstrated rigorously how the application of cold stimuli elevates pain thresholds. While the overall observations support the general concept of gating in the central nervous system (Head, 1921; Noordenbos, 1959; Wall, 1978), in the clinical context they contribute to a better understanding of symptoms in certain patients with peripheral neuropathies, and further clarify mechanisms of cold-induced analgesia. Similar findings and equivalent conclusions have been reported recently through study of direct nerve compression, without ischaemia (Wahren et al., 1989).

METHODS

Psychophysical thresholds

Subjective thresholds for cold sensation, warm sensation, cold-induced pain and heat-induced pain were measured during delivery of ramps of relatively low or high temperature stimuli using the Quantitative Thermotest (QTT) device (Somedic AB, Stockholm; Fruhstorfer et al., 1976). A Peltier type thermode measuring 2.5 × 5 cm was applied to glabrous skin at and adjacent to the thenar eminence of normal human volunteers. The temperature of the thermode could either rise or fall, from the adapting temperature of 32° C, at various rates, depending on the direction and intensity of the current flow through the Peltier device. The temperature range of the probe was 5–50° C. The subject held a switch in the free hand, which was to be pressed at the first sensation of either warmth, cold, heat pain or cold pain. Pressing the switch reversed the temperature of the probe, returning it to the adapting level. An Omniscribe chart recorder (D 5000, Houston Instruments, Austin, Texas) registered temperature changes with time. The rates of temperature change were 2° C/s when detecting low temperature-induced sensation, and 4° C/s when detecting low temperature-induced pain. Such rates drop exponentially as stimulus temperature departs from baseline. An illustration of an actual record is given in fig. 1.

Compression-ischaemia nerve block

After obtaining baseline threshold measurements, a sphygmomanometer cuff was inflated on the upper arm to a pressure of 80–100 mmHg above systolic blood pressure. Hand temperature was monitored on skin adjacent to the thermode, using a digital thermometer (2100 Tele Thermometer, VSI, Yellow Springs, Ohio). It was maintained within 1° C of baseline temperature by a radiating heat source. Compression-ischaemia was sustained for 1 h or until the volunteer requested release due to discomfort or pain underneath
COLD-INDUCED PAIN

Fig. 1. Actual QTT record of subject B.T., abbreviated to present only one response per stimulus series in only 5 series. In each series, the first deflection (left) is for cold sensation (CS), followed by warm sensation (WS), heat pain (HP) and cold pain (CP). After an initial threshold increase (distraction), cold pain thresholds decrease to peak at 30 min. Thereafter, thresholds increase again, that is, lower temperatures are required to reach threshold.

RESULTS

The study was performed on 19 volunteers, 7 males and 12 females, aged 19—50 (mean 34) yrs. The right hand was used in 12 subjects and the left in 7. Four volunteers kept the cuff on for a full hour while the other 15 failed to endure this duration because of local pain at the site of the cuff. Mean cuff time was 43.37 ± 2.36 (SEM) min (range 27—60 min). Mean time for loss of sensation evoked by light brushing of the skin was 21.68 ± 0.99 min. Subjects started reporting a change in the sensation induced by pin prick at 20.94 ± 2.53 min. This consisted of a transformation from sharp to dull pain in 14 subjects, to ‘something’ in 2 and to no sensation in 1. No change in the sensation induced by pin prick was reported by 2 subjects.

Cold sensation

In 14 subjects the quality of the first sensation evoked by a low temperature stimulus applied by the QTT probe changed at 21.14 ± 2.39 min (mean ± SEM). After this time, 11 described it as either hot (8) or burning (3), 1 as ‘something’ with no temperature quality, 1 as pain and 1 as a sting. Five other subjects kept reporting cold throughout the compression-ischaemia block period, which lasted 27, 33, 38, 42 and 60 min, respectively. However, in the first 2 of these 5 subjects, while the sensation of cold
induced by the thermode was unchanged, a sensation of cold was not induced by brief application of ice cube (at 23 and 17 min, respectively). This differential response suggests that these 2 subjects were on the verge of cold sensation block at the relatively early time of removal of the cuff.

When examining individual charts disclosing the evolution of threshold for the sensation of cold during the course of a block, the usual pattern was an early increase in threshold, in the first 5 min, which is thought to result from the distraction induced by the inflation of the cuff (Kojo and Pertovaara, 1986). Thereafter, thresholds for cold sensation became fairly stabilized for up to 15 min, beyond which they became elevated to reach eventually a final plateau at much lower temperature than baseline (fig. 1). As the timing for this change is different in different individuals, the details of this pattern are blurred in the averaged illustration (fig. 2), which shows a gradual threshold increase (reduction in

![Fig. 2. Mean cold sensation thresholds along the course of block (°C±SEM). Thresholds obtained at 45 min and later are drawn as open circles; they represent the few subjects that tolerated the cuff for that duration.](#)

required stimulus energy), reaching a plateau at about 25 min. The mean threshold at baseline was 30.46 ± 0.34°C. After 5 min mean threshold was 28.06 ± 0.33 and at 30 min of cuff 24.83 ± 0.91°C. Comparing either baseline thresholds or the results of 5 min with those at 30 min of block yielded a significant difference (P < 0.001, Wilcoxon test).

**Low temperature-induced pain**

The pain induced by a low-temperature stimulus ramp applied through the QTT probe changed in quality from ‘cold’ and usually ‘aching’, to ‘hot’ or ‘burning’ sensation in 13 of the 19 subjects at 20.36 ± 2.33 min. In 3 subjects the subjective response became pain without a thermal quality and in yet another 3 it remained unchanged throughout the test. Similar results were obtained by applying the ice cube: in 11 subjects the sensation became hot or burning (at 22.38 ± 1.31 min), in 4 it became pain with no thermal quality,
in 1 the ice induced a sensation of touch (at 24 min) and in 3 the sensation was unchanged throughout the block.

The mean baseline threshold for cold pain was $13.43 \pm 1.24 ^\circ C$. Following a slight increase in threshold immediately after cuff inflation, cold pain thresholds disclosed a biphasic profile of change (fig. 3). Stage I, as observed in 17 subjects, consisted of a gradual decrease in thresholds (pain was signalled at less low temperatures), reaching a peak at 27.3 min on average (range 15 – 55 min). The mean threshold at peak was $20.02 \pm 1.16 ^\circ C$, significantly different from the baseline value ($P < 0.001$, Wilcoxon signed rank test). Stage II was expressed in 15 subjects, and consisted of a weak reversal of thresholds towards baseline. The temporal relationship between the changes in thresholds for cold sensation and for cold pain is shown in fig. 4.

Two subjects failed to reveal any well defined trend in the evolution of their cold pain thresholds during the block.
DISCUSSION

The primary afferent channels conveying the neural message elicited by mild low-temperature stimuli are widely accepted as being subserved by small calibre myelinated fibres (A delta). This concept is based on direct stimulus response data obtained through recordings of physiologically identified single afferents in animals (Darian-Smith et al., 1973; Georgopoulos, 1976) and man (Adriaensen et al., 1983). Supporting evidence is provided by human psychophysical studies on cold sensation, either through differential nerve fibre blocks (MacKenzie et al., 1975; Fruhstorfer, 1976) or through reaction time measurement (Fruhstorfer, 1976; Fowler et al., 1988).

There is also evidence for participation of primary unmyelinated afferents in the conduction of impulses induced by low-temperature stimuli. Firing in animal C nociceptors in response to low-temperature stimuli, of both mild and noxious intensity, has been recorded by several investigators (Georgopoulos, 1976; Kumazawa and Perl, 1977; LaMotte and Thalhammer, 1982; Saumet et al., 1985), after other investigators had reported minimal or no response (Bessou and Perl, 1969; Croze et al., 1976). In man, only a handful of C nociceptors responding to cooling have been recorded (Torebjörk and Hallin, 1973; Yarnitsky and Ochoa, unreported observations).

Participation of A delta nociceptors in the transmission of impulses triggered by noxious cold stimuli has been described for the trigeminal system in animals (Jyväsjäervi and Kniffki, 1987; see review by Sessle, 1987) and is consistent with human psychophysical correlates of first and second cold pain (Kniffki et al., 1988). We believe that in the present study the cold pain message had no A delta nociceptor contribution since none of our subjects reported a double pain before or during the test, as did Kniffki’s subjects when exposed to noxious cold stimuli to their teeth.

We conclude, therefore, that when delivering a noxious low-temperature stimulus to our subjects, afferent activity was induced in two specific types of afferent channels, as suggested by LaMotte and Thalhammer (1982) and by Saumet et al. (1985). One type of channel conducts the cold message and is subserved by small myelinated A delta

Fig. 4. Mean thresholds for cold sensation (open circles) and cold pain (filled circles). After centring individual records, around the time of lowest threshold for cold pain (time 0), all thresholds along the time sequences were averaged. The increase in thresholds for cold sensation is clearly paralleled by the decrease in those for cold pain.
fibres, and the other conducts the pain message subserved by unmyelinated C nociceptors. Their cooperative actions result in the blended sensation of cold and usually aching pain.

Sensory processing during compression-ischaemia block might, in theory, be altered by cuff-induced pain and by metabolic ischaemic changes. However, the remarkable consistency of thresholds for heat-induced pain throughout the block session in all volunteers (Yarnitsky and Ochoa, unreported observations) indicates that in the present experiment pain perception was independent of these factors. Further, it was the subjective impression of all subjects that pain at the cuff site was clearly distinguishable from sensations evoked distal to it.

During A fibre block, a novel quality of pain, hot or burning, was induced by low-temperature stimuli applied either by the QTT probe or by an ice cube, a quality known to be induced by pure activation of human C nociceptors through intraneural microstimulation (Ochoa and Torebjörf, 1989). Since none of the subjects experienced this burning pain quality before block, when all pertinent afferent channels were available to conduct the message, it can be concluded that the afferent input normally elicited by noxious low temperature undergoes modulatory interaction. The burning subjective quality of the pain evoked by C nociceptors would normally be suppressed by another coexisting afferent barrage.

This interaction, moreover, not only affects the subjective quality attribute of the sensation, but it also affects its magnitude. Since with progressive block a sensory function should not be expected to improve, that is to reduce threshold, then the only reasonable explanation for the decreasing thresholds of pain induced by low temperature, as observed in stage I, is disinhibition. It may be hypothesized that under normal conditions, the neural message induced in myelinated fibres by a low-temperature stimulus inhibits the message evoked in unmyelinated fibres by the same stimulus. Although the most likely channel to exert this gating is the cold-specific channel, the present results cannot exclude involvement of other myelinated channels activated by this stimulus. Previous evidence by Bini et al. (1984) showing an increase in intraneurally-induced pain thresholds by cooling the cutaneous projective field also suggests that the cold-specific channel exerts pain inhibition.

As block progresses and myelinated afferent channels are less and less available, the inhibition becomes weaker, allowing the cold pain threshold to decrease, although enough cold-specific afferents are still available to mediate a residue of cold aching pain. Next, the cold-specific channels are closed, and the message induced by noxious low temperature is carried exclusively by nociceptors. This releases a burning pain, at a relative low threshold, demonstrated as the peak threshold in fig. 3. Later, as C nociceptors themselves start blocking, in order to compensate for loss of spatial summation, increased temporal summation is needed to reach threshold for pain. This explains the increasing thresholds for cold pain in stage II.

The general idea of central ‘gating’ of sensory information has been entertained by sensory physiologists for decades (Head, 1921; Noordenbos, 1959; Wall, 1978). More specifically, gating of the input of C nociceptors that convey the pain fraction of the cold pain message, exerted by cold-specific A delta afferent input carrying its cold
fraction, was proposed by LaMotte and Thalhammer (1982) as an explanation for the observation that monkey C nociceptors fire in response to presumably innocuous low temperature stimuli (20° C). Further evidence was contributed by Bini et al. (1984), as described previously. Those results support our assumption, discussed above, that of the sensory submodalities served by myelinated fibres, it is the cold-specific input that exerts the gating. This mechanism provides an alternative to Fruhstorfer's proposal of the existence of a special class of low threshold, \textit{cold-specific} unmyelinated receptors sensing a 'dysaesthetic' cold sensation when myelinated fibres are blocked (Fruhstorfer, 1984). Instead, it is proposed here that the high threshold C nociceptors evoke a pure unblended pain quality, at a reduced threshold, due to removal of modulation normally exerted by the A delta myelinated mediated fraction of the cold pain message. A recent study (Wahren et al., 1989) used direct nerve compression as a means of blocking A fibres selectively, and reached similar conclusions regarding the qualitative and quantitative changes in the perception of pain induced by low-temperature stimuli. Admittedly, the present results have been interpreted strictly in accordance with the specificity theory of somatic sensation, and in these terms the explanation seems highly plausible. The authors find it difficult to reconcile the results in terms of pattern theory.

Disinhibition is not the only mechanism for low temperature to suppress pain. Cooling can disable the sensory apparatus by either blocking nerve impulse conduction (Franz and Iggo, 1968) or by desensitizing normal receptors (Kunesch et al., 1987). Such effects are probably not pertinent to the present study, since in the experiments of Franz and Iggo temperatures below 10° C were applied directly to the nerves, and in the study by Kunesch \textit{et al.}, prolonged cooling for at least 3 min was applied. Such extreme conditions were not used in our study; QTT probe temperature seldom dropped below 10° C, and stimulation time was less than 30 s, while application time of ice cube was less than 10 s.

An abnormally released interaction between the two channels—cold-specific and nociceptor-specific—is perhaps expressed in certain neuropathic pain patients who complain that their symptomatic limbs 'burn' when cold. Quantitative sensory testing of thermal specific and thermal pain thresholds from limbs of such patients shows the low-temperature stimulus to be perceived as warm-burning, associated with elevated cold sensation thresholds, suggesting functional deficit of cold related A delta fibres. A noxious low-temperature stimulus may thus induce an ungated pain message, evoking a sensation of burning pain (Ochoa and Yarnitsky, 1990). The observation by Kashihara and Yabuki (1987) that in 2 patients with Guillain-Barré syndrome, low-temperature stimuli were felt as burning, can also be explained by the proposed mechanism, since the disease process is expected to disrupt function in the cold-specific A delta myelinated fibres, but not the nociceptor unmyelinated fibres.

In conclusion, psychophysical evidence is hereby raised to support the hypothesis that when a noxious low-temperature stimulus is given, the cold-specific message gates the pain message, 'protecting' the subject from excessive pain. In other words, cooling may be an active way to relieve pain.
ACKNOWLEDGEMENTS

This study was supported by NIH grants RO1 NS 24740 and 24766. Informed consent of the subjects was obtained.

REFERENCES


(Received January 13, 1989. Revised July 4, 1989. Accepted July 24, 1989)