DIFFERENTIAL EFFECT OF COMPRESSION-ISCHAEMIA BLOCK ON WARM SENSATION AND HEAT-INDUCED PAIN

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SUMMARY

The effect of compression-ischaemia nerve block on psychophysical thresholds for warm sensation and heat-induced pain was studied on 19 normal human volunteers. Although those two sensory submodalities should be predicted to block simultaneously, based on the fact that both are served by unmyelinated primary afferents, it was actually found that warm sensation was much more vulnerable to compression-ischaemia than heat-induced pain. This is interpreted as resulting from different summation requirements for each of the two sensory modalities; sensation of warmth depends on spatial summation to a larger extent than heat-induced pain. Such differential vulnerability is in line with recent clinical studies reporting deterioration of warm sensation associated with preservation of heat pain in peripheral nerve disorders caused by diabetes, ageing and other neuropathic processes.

INTRODUCTION

Application of a constricting force to a nerve is a time-honoured method for blocking nerve fibres differentially (Bastien and Vulpian, 1855 (direct pressure to several human nerves); Gasser and Erlanger, 1929 (cuff, in vitro, animals); Lewis et al., 1931 (cuff, humans); Zotterman, 1933 (cuff, humans); Gasser, 1935 (cuff, in vivo, cat); Sinclair and Hinshaw, 1950 (cuff, humans, and literature review), and others). The relationship between time to block and the type of nerve fibre subpopulation blocked has been established electrophysiologically. Under direct nerve compression in vitro, fibres of similar conduction velocity stop conducting nerve impulses at the same stage along the course of the block, fast A fibres blocking first and slow C fibres last (Gasser and Erlanger, 1929). Early loss of impulse propagation in myelinated A fibres in experimental animals during direct nerve compression, or whole limb compression-ischaemia blocks was indirectly correlated with human psychophysical studies, revealing corresponding early abolition of perception of tactile and cold stimuli (see Sinclair and Hinshaw, 1950). Thus tactile and cold sensations can be accepted as being subserved by myelinated primary afferents, while the residual sensations of warmth and pain are accepted as subserved by unmyelinated fibres, as both disclose similar resistance to block (Lewis et al., 1931; Sinclair and Hinshaw, 1950). Eventually these claimed associations between sensations and fibre types were directly confirmed microneurographically in awake humans (Torebjoerk and Hallin, 1973; Mackenzie et al., 1975; Hallin et al., 1982).

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If a compression-ischaemia block were maintained long enough to interfere with conduction of unmyelinated fibres, similar blocking times for warm sensation and heat pain should be anticipated in theory since the corresponding primary afferents conduct at a similar velocity in humans (Konietzny and Hensel, 1975; Torebjörk et al., 1984). Nevertheless, our results show that at a stage when thresholds for warm sensation are significantly elevated, those for heat pain are still unchanged.

METHODS

Sensory testing

Routine clinical sensory examination included (1) evaluation of light touch tested by weak mechanical stimuli applied by stroking with a fine brush; (2) evaluation of mechanical pain, tested by intense mechanical stimuli applied by pin prick; and (3) evaluation of cold-specific sensation tested by surface application of an ice cube. All tests were performed on hairy skin on the dorsum of the hand.

Quantitative testing of thermal-specific and thermal pain submodalities (warm sensation, cold sensation, heat-induced pain and cold-induced pain) was performed by measuring thresholds during delivery of ramps of relative high or low temperature stimuli using the Thermotest (Somedic AB, Stockholm), as described by Fruhstorfer et al. (1976). A Peltier type thermode measuring 2.5 X 5 cm was applied to glabrous skin at the thenar eminence of normal human volunteers. Temperature of the thermode could either rise or fall, at various rates, from the adapting temperature of 32°C, depending on the direction and intensity of the current flow through the Peltier device. The subject held a switch in the free hand, 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) reproduced the results graphically. The rates of temperature change were 1.2°C/s for warm sensation and 3°C/s for heat pain.

Compression-ischaemia nerve block

After obtaining baseline threshold measurements, a sphygmomanometer cuff was inflated at upper arm level to a pressure 80-100 mmHg above systolic blood pressure. Hand temperature was monitored on the 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 which counteracted the tendency towards cooling during ischaemia. Compression-ischaemia was sustained for 1 h or until the volunteer requested release due to discomfort or pain underneath the cuff. Thermotest threshold measurements were performed cyclically throughout the test session, supplemented by clinical sensory testing. In addition to signalling thresholds, the subject was instructed to describe verbally sensations evoked by the various stimuli. In order to avoid anticipatory reactions, the sequence of presentation of the thermal stimulations was changed randomly from one cycle to the other. However, the two thermal sensations always preceded the two thermal pains. Since individual measurement times differ, all results were grouped to the nearest 5 min and then averaged. Results pertaining to low temperature stimulation are reported separately (Yarnitsky and Ochoa, 1990a).

RESULTS

The study was performed on 19 healthy volunteers, 7 males and 12 females, aged 19-50 (mean 34) yrs, all of whom gave informed consent. The right hand was used in 12 subjects, the left in 7. Four volunteers tolerated the cuff for a full hour while the other 15 failed to endure this length due to local pain at the site of the cuff. Mean cuff time was 43.37 ± 2.36 (range 27-60) min, all results being given as mean ± SEM.

The sensation evoked by light brushing of the skin was lost at 21.68 ± 0.99 min of block. Subjects started reporting a change in the sensation induced by pin prick at 20.94 ± 2.53 min. This consisted of transformation from sharp to dull pain in 14, to
‘something’ in 2 and to no sensation in 1. No change in the sensation induced by pin prick was reported by 2. A mild low temperature stimulus was no longer perceived as cold beyond 21.14 ± 2.39 min by 14 subjects and the ice cube was not perceived as cold beyond 20.36 ± 2.33 min in 13 subjects.

Warm sensation

After a small initial increase in thresholds (from 33.15 ± 0.15 at baseline to 34.01 ± 0.20 at 5 min of block), which could be related to the distraction surrounding cuff inflation (Kojo and Pertovaara, 1986), thresholds for warm sensation increased very gradually over 25 min. By that time a definite increase of threshold was observed, reaching 37.37 ± 0.44° C at 40 min of cuff (fig.). Mean thresholds at 5 and 40 min were significantly different (P = 0.0016, Wilcoxon Signed Rank test).

The quality of sensation evoked by a mild high temperature stimulus was unchanged in 14 subjects, while in the remaining 5 subjects sensations of ‘something’, pain, sting, sharp and burning were reported during the block.

Heat pain

Mean thresholds for pain induced by heat were essentially unchanged throughout the test (fig.). Baseline measurement revealed a mean threshold of 41.61 ± 0.63° C. During the cuff session, mean threshold varied between 41.20 ± 0.67 (at 5 min) and 41.73 ± 0.58° C (at 25 min).

The painful sensation reported when delivering a noxious hot stimulus was quite resistant to block. One subject lost the heat quality at 34 min, but kept reporting pain, and another started reporting ‘sting’ at 23 min. The other 17 subjects kept reporting heat pain throughout the block.
DISCUSSION

The distinct sensations of warmth and delayed pain have traditionally been correlated with conduction in unmyelinated primary afferents (see Sinclair and Hinshaw, 1950, for a review). Indirect evidence supporting this concept has been raised through experimental differential nerve blocks. Direct nerve compression and whole limb compression-ischaemia blocks applied to humans result in abolition of the sensations of touch and cold very close in time to the abolition of impulse propagation in myelinated fibres under similar block in animals. Beyond this stage of block, warmth and pain are still perceived while the only available afferents in the animal model are unmyelinated fibres (Lewis et al., 1931; Gasser, 1935; Sinclair and Hinshaw, 1950). Dyck and Lambert contributed clinical-pathological evidence supporting these correlations by showing (1) striking loss of large myelinated fibres in disease states that feature loss of perception of light touch (1968), and (2) loss of unmyelinated fibres in amyloid neuropathy in patients with loss of temperature and pain sensation (1969). Through the use of microneurography, relationships between sensory submodality and afferent fibre type have been confirmed directly in humans during differential nerve blocks (Torebjörk and Hallin, 1973; Mackenzie et al., 1975).

Eventually, direct nerve recordings in animals and humans established the subdivision of unmyelinated primary afferents into (1) warm specific units, responding exclusively to mild, nonnoxious temperature elevation (Konietzny and Hensel, 1975; Darian-Smith et al., 1979; Duclaux and Kenshalo, 1980) and (2) polymodal nociceptor specific units that fire in response to intense mechanical and thermal stimuli inclusive of noxious heat (Torebjörk, 1974; Hallin et al., 1982; Van Hees and Gybels, 1981). These two subsets of fibres have similar conduction velocities, and therefore can be taken to have similar axon calibres, although direct morphometric studies of functionally identified unmyelinated afferents in humans remain to be obtained.

Surprisingly, dissociated clinical behaviour has been reported recently for the sensations related to these two groups of unmyelinated primary afferents. The ability to sense warm stimuli may be significantly reduced while no change is detected in the ability to sense heat pain stimuli in the elderly (Kenshalo, 1986; Mitchell and Schady, 1988), in diabetic patients (Claus et al., 1987; Ziegler et al., 1988a, b; Navarro et al., 1989) and in various types of neuropathic patients (J. Ochoa and U. Lindblom, unpublished observations). Assuming that primary afferents of similar structural properties are bound to be equally affected by systemic degenerative processes, such dissociated impairment of function calls for explanation.

One possibility assumes different central spatial summation requirements for the sensory channels concerned, such that during progressive and equivalent depopulation of functioning primary afferents a point in time comes when weak summation jeopardizes the sensation that requires it most. Several studies have been conducted on the spatial summation requirements for sensations evoked by high temperature stimuli. Lele (1954), Kenshalo et al. (1967), Stevens et al. (1974) and Kojo and Pertovaara (1987), all demonstrated strong dependence of warm-specific perception thresholds on the area of stimulation; thresholds decreased as stimulus area increased. The effect of stimulus area on heat pain thresholds is less clear. Machet-Pietropaoli and Chery-Croze (1979) and Kojo and Pertovaara (1987) found a similar inverse relation between heat pain thresholds and stimulus area, but Greene and Hardy (1958) found heat pain thresholds
to be only minimally affected by stimulus area, and Stevens et al. (1974) also found the stimulus area factor to be negligible for hot stimuli at pain threshold intensity. More recently it has been shown that selective intraneural stimulation of a few unmyelinated nociceptors can be sufficient to induce a delayed burning pain (Ochoa and Torebjörk, 1990), whereas warm sensation cannot be induced by weak intraneural microstimulation, implying a significant spatial summation requirement (see Ochoa, 1984).

Another possible explanation for the dissociated behaviour of warm sensation versus heat pain might be a relatively smaller number of warm-specific units, compared with C nociceptors (Handwerker and Neher, 1976; Hallin et al., 1982; Saumet et al., 1985). Even if the two submodalities had similar spatial summation requirements, such that equivalent depopulation of their primary afferents (by disease or experimental block) would cause equivalent elevation of thresholds, the numerically underrepresented warm-specific afferent function would defect earlier below a critical level.

Differences in receptor susceptibility to ischaemia may be a contributing factor in determining the response to block. While resistance of rabbit polymodal nociceptors to a short period of ischaemia was demonstrated by Lynn (1979), the behaviour of warm-specific units has not, to our knowledge, been tested under those circumstances. This possibility remains open.

Although there exists evidence for participation of small myelinated A-delta fibres, in addition to unmyelinated nerve fibres, in conduction of impulses induced by a noxious hot stimulus (Lewis and Pochin, 1937; Price et al., 1977; Campbell and LaMotte, 1983), for all practical purposes the sensation of heat pain, as probed in the present study, is a C fibre conducted submodality. Indeed, we tested thermal sensations in glabrous skin quantitatively, where both microneurographic (Torebjörk and Ochoa, unpublished) and psychophysical (Campbell and LaMotte, 1983) data fail to demonstrate responsiveness of A delta fibres to the stimulus at intensity near heat pain threshold. Moreover, even in hairy skin, at the relatively low rate of temperature rise used to evoke heat pain in the present study, reaction time measurement indirectly indicates peripheral conduction in the unmyelinated fibre range of velocity (Yarnitsky and Ochoa, 1990b).

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