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THE SENSITIZATION OF HIGH THRESHOLD MECHANORECEPTORS WITH MYELINATED AXONS BY REPEATED HEATING

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SUMMARY

1. Seventy high threshold mechanoreceptor units (HTMs) with myelinated axons were isolated from the sural nerves of cats and rabbits. Thirteen cat and forty-two rabbit HTMs were tested by controlled, repeated heating of the skin of the foot or lower leg to noxious levels.

2. Many of the units (77 % in the cat and 40 % in the rabbit) fired to heating. Only six (11 %) of these fired to the first brief heating to 50–55° C. The rest required 2–6 heat trials before responding.

3. Heat responding units always became more sensitive with repeated heat stimulation but their mechanical sensitivity showed no comparable changes when heat sensitization occurred.

4. If these results are applicable to man, they suggest that HTMs play little role in generating the first pain that follows skin heating but that they may be involved in the increased sensitivity to heat pain (hyperalgesia) shown by skin previously injured by heating.

INTRODUCTION

Two main types of high threshold, presumably nociceptive, afferent units have been described in mammalian skin. These are (1) high threshold mechanoreceptor units (HTMs) with receptive fields consisting of a number of discrete points and with small myelinated axons and (2) polymodal nociceptor units with receptive fields comprising one small zone and with unmyelinated axons. In the first detailed investigations of these units another important distinguishing feature was that polymodal nociceptors fired readily on heating the skin to noxious levels (Bessou & Perl, 1969) whilst HTMs showed no such responses (Burgess & Perl, 1967; Perl, 1968). Subsequent studies of HTMs have, however, found that many are heat responsive (Beck, Handwerker & Zimmermann, 1974; Georgopoulos, 1976). One possible reason for the discrepancy between different studies is

that HTMs have been reported to become heat sensitive if the skin is subjected to a substantial period (many seconds) of heating to temperatures of 50–55° C (P. R. Burgess & D. Whitehorn, unpublished data cited by Burgess & Perl, 1973). Thus differences in the extent of a previous heating of a skin region could give rise to contrary observations on the heat sensitivity of HTMs.

In the study reported here, we have investigated the heat sensitivity of HTMs in the hairy skin of cats and rabbits using carefully controlled sequences of stimuli. Care was taken to avoid any stimulus which might cause sensitization before the first heat test. The sensitivity of HTMs to controlled mechanical stimulation was also examined both before and between heat stimuli. Our results show that although HTMs rarely fire to the first heat trial, many HTMs do respond after the skin has been heated several times, in both cat and rabbit. The possible role of HTMs in transmitting information about heat pain is discussed.

METHODS

Preparation. The experiments were carried out on anaesthetized cats and rabbits. Rabbits were anaesthetized with urethane (1·8 g/kg) administered through the marginal ear vein; cats were anaesthetized with pentobarbitone sodium (Nembutal, Abbott Labs), initially I.P. (40 mg/kg) and subsequently I.V. through the external jugular vein. A tracheal cannula was inserted. The rectal temperature was monitored and maintained between 36·5 and 38·5° C. The sural nerve was exposed in the popliteal fossa for recording and electrical stimulation. In a few cat experiments the accessory sural nerve was also used. Small filaments were dissected from the nerve under light liquid paraffin and placed over fine platinum wire electrodes. An indifferent electrode was placed on the whole nerve. One to 3 cm distal from the recording site the nerve was placed over a pair of platinum wires for electrical stimulation. The leg was fixed by clamping the toes and sometimes by placing a pad beneath the ankle. The hair was left full length until a receptive field was approximately defined whereupon the hair on the field was clipped short.

Heat stimulator. Receptive fields were heated using a small projector bulb with a built-in reflector (Fig. 1). A spring mounted copper-constantan thermocouple was pressed gently on to the skin near the centre of the beam from the lamp. The lamp was usually positioned such that an area about 1 cm in diameter was heated. Sometimes the area heated was restricted by shielding parts of the skin with aluminium foil. The lamp was controlled by a servo system which compared the temperature from the skin thermocouple with a reference signal and adjusted the power supplied to the lamp appropriately. The automatic control system allowed the skin to be held at any temperature between its resting value and about 65° C with an accuracy of better than 0·3° C. Usually a stimulus sequence consisted of an initial holding period of a few seconds at a temperature 1–3° C above the resting value, followed by a steady increase at 1° C/sec to another holding temperature. Often, however, the stimulus consisted of only a ramp increase in temperature from resting to a pre-set maximum, and then its immediate cessation.

The skin thermocouple pressure made a slight difference to the recorded skin temperature. With unstimulated skin, the reading changed by less than 1·0° C

for forces from 0·03 to 0·08 N and the spring mount for the thermocouple was adjusted so that the force exerted on the couple was in this range. The thermocouple itself did not absorb a significant amount of heat when the lamp was on since raising it just off the skin caused an immediate drop in the recorded temperature of at least 5° C.

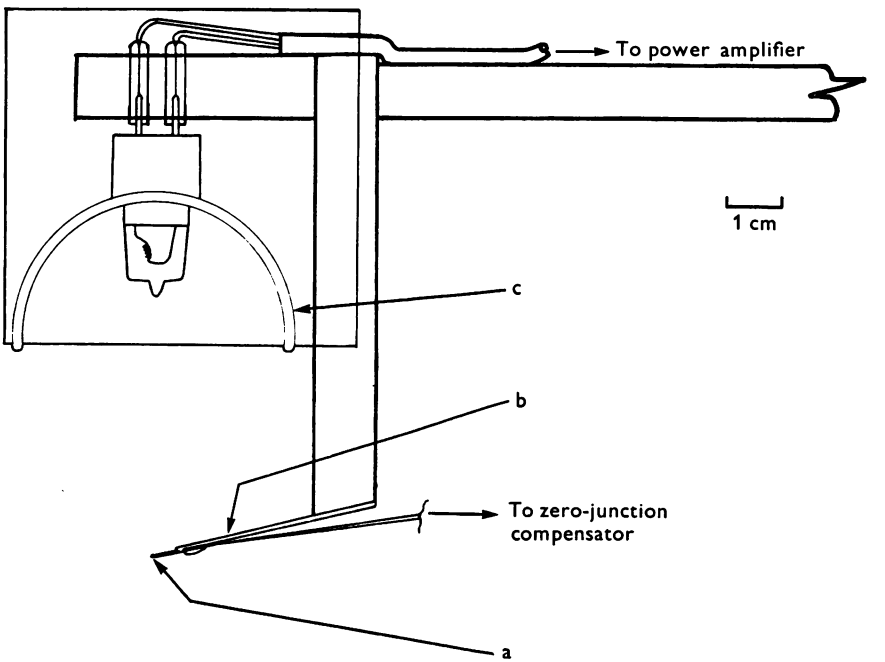

Fig. 1. Radiant heat stimulator. a, copper-constantan thermocouple, made from welded 0·2 mm diameter wires (type 6, Delristor Ltd) or by soldering two 43 swg wires; b, flat brass spring; c, projector lamp with integral reflector (type A1/231, 12 V, 100 W, Atlas or G.E.C.). The stimulator was positioned with the thermocouple pressing gently on the skin. To produce a particular skin temperature change, or to maintain a fixed temperature, the signal from the thermocouple was compared with a reference signal and the difference was fed to the lamp power amplifier.

Mechanical stimulator. The mechanical stimulator is shown in Fig. 2. A low inertia DC motor drives a radial arm which is long enough to reach the centre of a receptive field when the heat stimulator is also in position. The force of a stimulus was monitored by two silicon strain gauges stuck to the arm. The motor was normally used under servo control. The signal from the strain gauges was compared with a reference voltage and the error signal was amplified to drive the motor. Connexions to the motor were made by wires soldered directly to the armature. Variable derivative feed-back was also obtained by differentiating the force signal from the stimulator. The amount of derivative feed-back was adjusted to obtain suitably damped stimuli for a particular load. The maximum force available was 1·0 N, and the resolution of the monitoring system was 0·5 mN. Stimuli could be applied at a rate of up to 0·5 N/sec.

The force needed to excite mechanoreceptors was greater with the motorized stimulator than with the von Frey hairs used for preliminary exploration of receptive fields. This was because the von Frey hairs had ends that were considerably smaller (0·1–0·4 mm diameter) than the end of the stylus of the motorized stimulator.

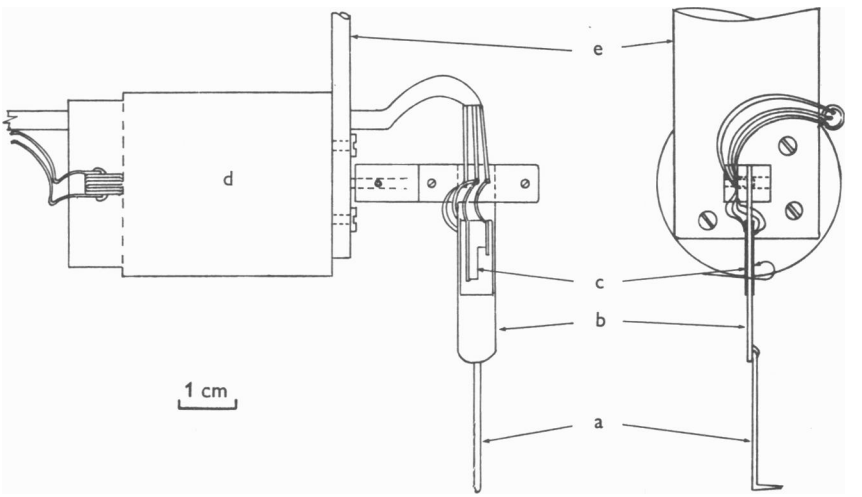

Fig. 2. Mechanical stimulator. a, stylus that pressed perpendicularly on the skin. End was circular with a diameter of 0·8 mm; b, flat steel spring, thickness 0·7 mm; c, silicon strain gauges (type 3A-1A-350P, Ether Ltd), one on each side of the spring; d, low inertia DC motor (Maxon, Type 2132, 908). Note connexions direct to armature; brush assembly has been removed; e, mounting bracket. The stalled torque of the motor is 0·05 N m, so with the 5 cm arm shown forces of up to 1·0 N could be generated.

RESULTS

General properties of cat and rabbit HTM units

A total of 219 units were isolated from the sural nerve and classified according to conduction velocity, receptive field type and adequate stimulus: 159 units were from the rabbit and sixty from the cat. Of these, fifty-two rabbit units and eighteen cat units were classified as HTMs. Our sample of units is very biased towards those with high thresholds, and many nerve filaments containing only hair units were not examined in detail. Further, it is much easier to isolate large axons than small ones. Consequently the above figures give little indication of the true proportion of HTM units in the sural nerve. However, in this preparation there did appear to be a larger proportion of high threshold to low threshold mechanoreceptors in the rabbit than in the cat.

Receptive fields. The rabbit sural nerve innervates the lateral leg from below the knee to the ankle and the lateral side of the proximal half of the

foot. The sural nerve in the cat innervates only the equivalent ankle and foot areas whilst the accessory sural nerve innervates the lateral leg area. So to obtain a comparable distribution of unit receptive fields both sural and accessory sural were used in the cat. The fields of HTM units were spread over the entire field of the relevant nerves (see Fig. 3*A*).

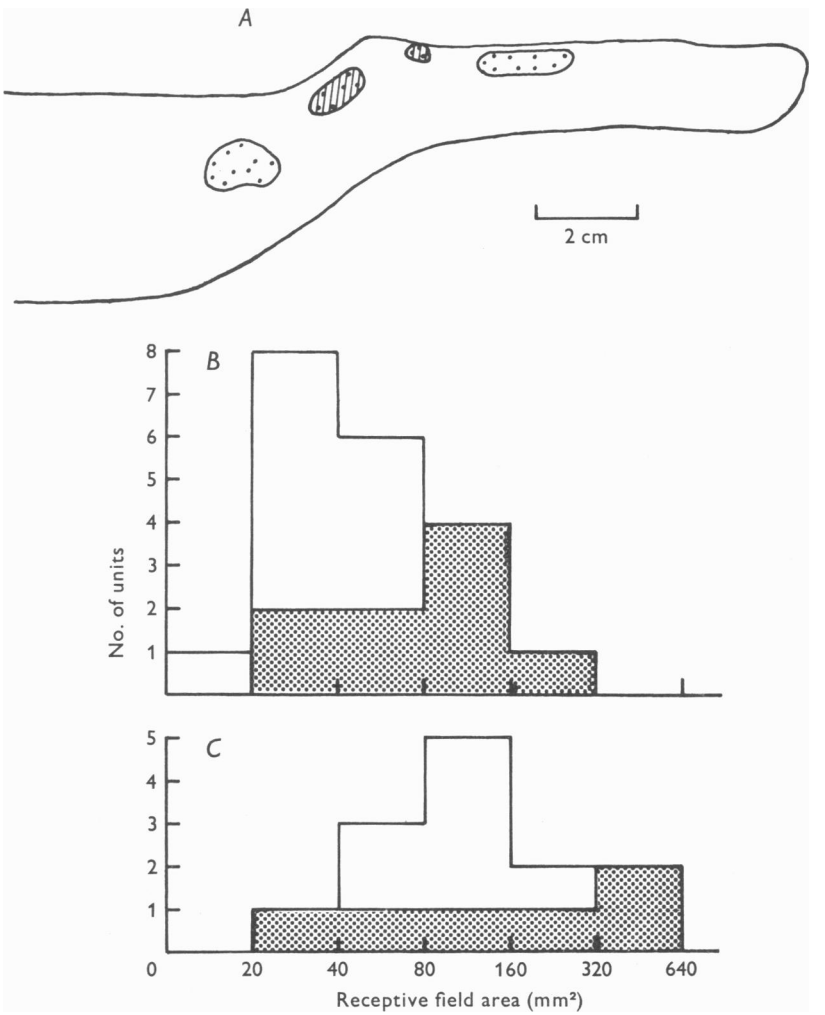

Fig. 3. Receptive fields of high threshold mechanoreceptor units (HTMs) in the rabbit and cat. *A*, four representative fields, two from the cat and two from the rabbit (cross hatched). *B*, frequency distribution of the areas of twenty-eight rabbit receptive fields. Stippling: fields on the leg; open: fields on the ankle and foot. Note logarithmic scale for area. *C*, as *B*, but for thirteen cat HTMs.

The fields were mostly approximately elliptical in shape with the longer axis running in the proximal–distal direction. In the rabbit the areas of receptive fields ranged from 0·18 to 2·60 cm^2 and the frequency distribution is shown in Fig. 3*B*. All fields were punctate with 2–16 sensitive spots;

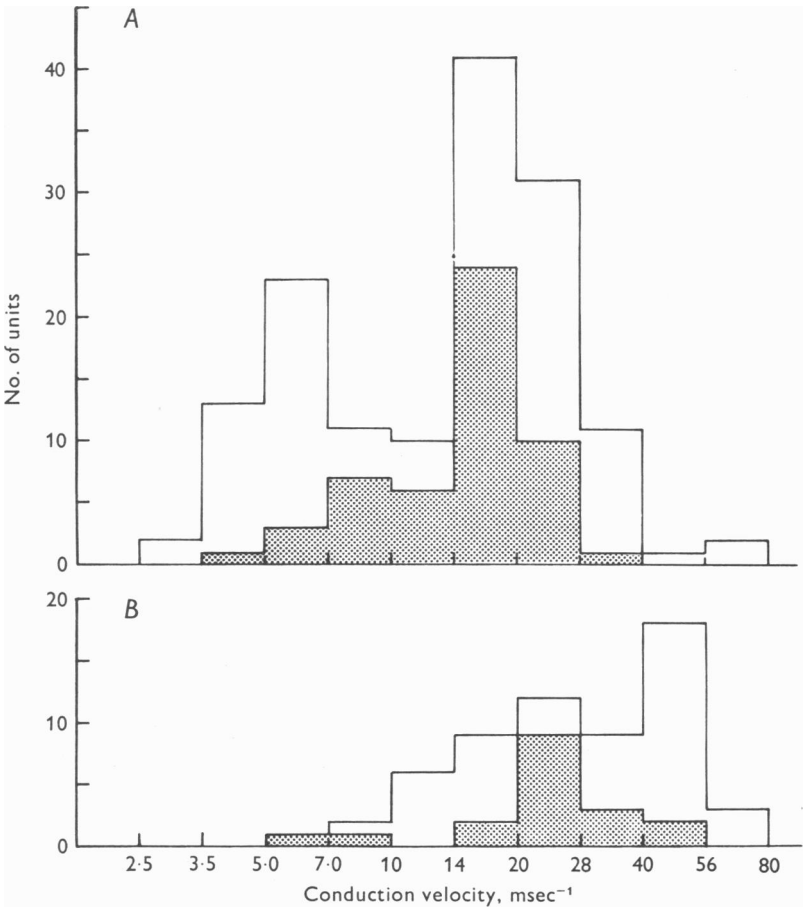

Fig. 4. Conduction velocities of 146 rabbit (*A*) and sixty cat (*B*) myelinated fibres isolated from sural and accessory sural nerves. Stippled areas give frequency distributions for HTMs; unstippled parts are for all other units with myelinated axons (these were mostly hair units). Note: (1) logarithmic velocity scale, and (2) that this is *not* a random sample of all the myelinated fibres in the nerves studied.

the number of spots per cm^2 varied from 5–20. There was a clear difference in the rabbit between receptive fields on the leg and those on the foot and ankle, the former being significantly larger ($P < 0·01$, Mann–Whitney test (Mosteller & Rourke, 1973)).

Cat HTM receptive fields ranged from 0·4 to 4·1 cm^2 in area and there was no difference between leg, ankle and foot fields as shown in Fig. 3*C*. Fields on the cat foot were therefore greater in area than those on the rabbit foot ($P < 0·05$, Mann–Whitney test). There was no difference between the sizes of cat and rabbit fields on the legs.

Conduction velocity. In the rabbit, the conduction velocities of forty-two nerve fibres of HTM units ranged from 5·0 to 32·5 m/sec and the average velocity was 15 m/sec. The frequency distributions of conduction velocities of HTMs and of other units with myelinated fibres are shown in Fig. 4*A*. As found by Brown & Iggo (1967), conduction velocities in the cat were higher, both for HTMs and for other types of unit. HTM conduction velocities ranged from 5·5 to 49 m/sec and averaged 27 m/sec in the cat (see Fig. 4*B*). The difference between HTM conduction velocities in cat and rabbit is statistically significant ($P < 0·01$, Mann–Whitney test).

Thresholds for mechanical stimulation. The mechanical thresholds of many HTMs were measured using a series of calibrated von Frey hairs. The stiffest bristle exerted a force of 50 mN, and this was sufficient to excite thirty-seven out of thirty-eight rabbit HTMs and eight out of thirteen cat HTMs.

There was no discernible relation between von Frey thresholds and either receptive field size or location. As reported by Burgess & Perl (1967), there was a slight tendency for more sensitive units to have faster conducting axons.

A few units (eleven in the rabbit, two in the cat) were isolated that could be excited by electrical stimulation of the nerve but could not be excited by mechanical stimulation of the skin. Possibly some of these units were even less sensitive than those described above and required a stimulus that penetrated the skin before firing. We did not use this form of stimulation since we wished to test heat sensitivity in undamaged skin later on. The conduction velocities of the inexcitable units in the rabbit were fairly low and ranged from 4 to 23 m/sec (average 11 m/sec).

Mechanical responses

Stimulus–response relations were obtained for most units by applying a series of stimuli of varying force at one minute intervals using a servo-controlled stimulator. The stimuli were applied at a constant rate, usually approximately 0·1 N/sec, with the stimulator stylus positioned perpendicularly to the skin surface over one of the sensitive points in the receptive field. The usual response criterion was the number of spikes fired during the first 2·5 sec of steady pressure. Many rabbit units fatigued, thus causing successive responses to vary considerably. Also, a very large stimulus sometimes appeared to increase the sensitivity of a unit to the next

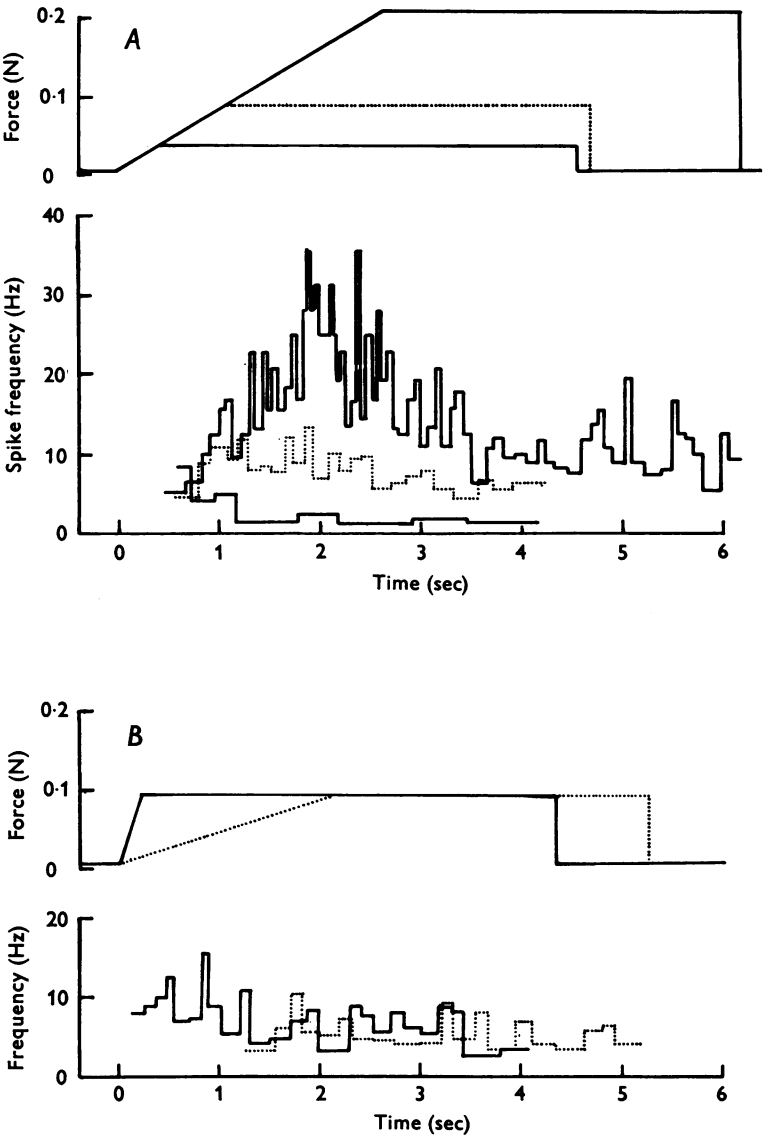

Fig. 5. *A*, responses of cat HTM to different stimulus amplitudes. Upper traces, stimulus force. Lower traces, firing pattern plotted as instantaneous frequency. The height of each bar represents the reciprocal of the interval between two successive spikes.

B, responses of the same unit as in *A* to stimuli applied at different rates. Traces as in *A*.

stimulus. As a result, stimulus–response curves showed considerable scatter (see Fig. 5*A*). It is possible that some of the variability is related to small movements of the skin that might lead to a change in the point of stimulation and therefore to an apparent change in responsiveness.

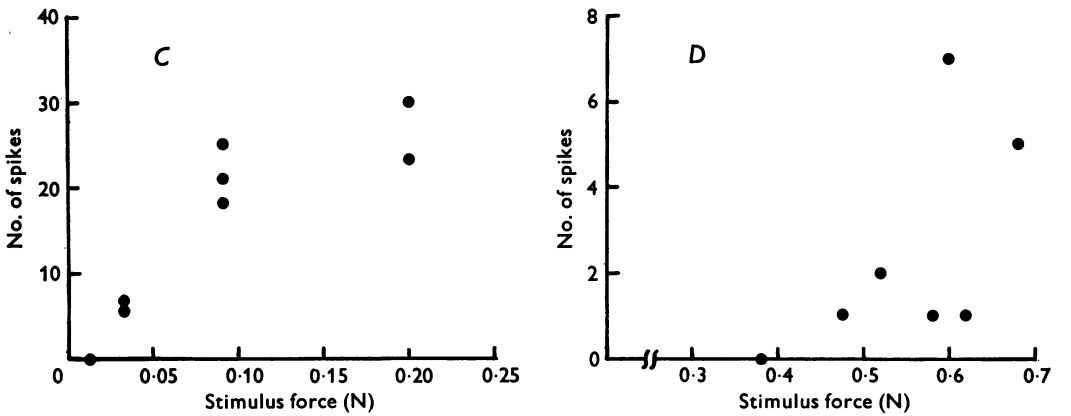

Fig. 5. *C*, stimulus-response relation for the cat HTM whose discharges are shown in *A* and *B*. Abscissa: stimulus force; ordinate: number of spikes in first 2·5 sec of steady force. Rate of onset 0·086 N/sec as in *A*.

D, stimulus–response relation for rabbit HTM. Axes as in *C*. Note considerable variability; this was typical of rabbit units.

The cat units were less variable in their responses to mechanical stimulation. A stimulus–response curve and a representative set of records are shown in Fig. 5*A–C*. The instantaneous frequency plots in Fig. 5*A* show the slow adaptation of firing that was commonly observed during stimulation with a steady force. Not all units showed this adaptation, and some units did the opposite, gradually increasing their firing during a maintained stimulus.

A number of units were tested with stimuli that had a constant amplitude but different rates of rise in the range 0·03–0·5 N/sec. A typical set of traces is shown in Fig. 5*B*. HTM units did not show very marked velocity sensitivity, but they did usually fire more rapidly during the onset of a rapidly applied stimulus than either during the subsequent hold or during the onset of a stimulus with a longer rise time.

Heat sensitivity

Proportion of heat sensitive HTMs. The heat sensitivity of forty-two rabbit and thirteen cat HTMs was tested by a series of controlled stimuli at 3 min intervals. Care was taken to ensure that there had been no previous heating of the receptive field. Occasionally units were studied

whose fields were immediately adjacent to areas damaged by previous heating or strong mechanical stimulation, but in general such units were discarded. The first two to five stimuli raised the skin temperature to 48–55° C at a rate of 1° C/sec. The skin was not held at the peak temperature. If these brief stimuli failed to evoke a response, then during the next two to six heatings the skin temperature was held at 50–55° C for 10–30 sec. If the unit still failed to fire, the skin temperature was raised to 60° C and held there for up to 60 sec. When a unit did fire, the peak temperature of the subsequent stimuli was kept the same or sometimes reduced as seen in Figs. 6 and 7.

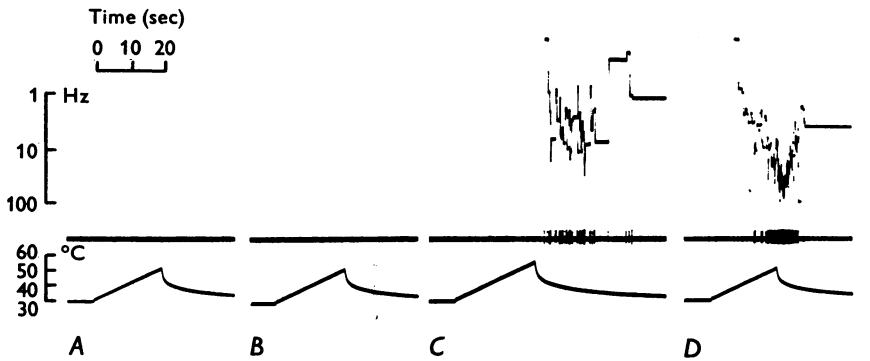

Fig. 6. Heat responses of rabbit HTM. The first two heat stimuli to 50° C (*A*, *B*) fail to produce any firing. The third stimulus (*C*), to 55° C, produces some firing immediately after the heating has ceased. The fourth stimulus (*D*), to 50° C, produces vigorous firing both during heating and for some seconds afterwards. Bottom traces: skin temperature; middle traces: action potentials recorded from the sural nerve; top traces (*C* and *D* only): 'instantaneous' log interspike interval display of the discharges. (N.B. the trace is held at the appropriate level for a given interspike interval for the whole of the next interval.)

Seventeen out of forty-two rabbit HTMs (40 %) showed clear and repeatable responses at some time during the procedure. Ten out of thirteen cat HTMs (77 %) fired during the heating tests, a proportion that is significantly higher than in the rabbit ($X^2 = 6{\cdot}63$, d.f. $= 1$, $P = 0{\cdot}01$).

In other respects units that responded to heating resembled those that failed to respond. They were distributed throughout the innervated region and their receptive field areas, conduction velocities and mechanical thresholds were similar.

Sensitization following repeated heating. The most striking aspect of the heat responses of HTMs was that they all showed sensitization, i.e. their responses to heating increased on successive heat trials. In fact the majority of units did not fire to the first heat trial and some only started firing after

six previous stimuli to 50 or 55° C. Possibly even more units would have shown heat responses had we persisted with non-destructive heating even longer.

Of the seventeen heat responsive units found in the rabbit, only three fired to the first heat stimulus and they were all found towards the end of an experiment when nearby areas of skin had already been subjected to considerable heating and to vigorous mechanical stimulation. In the cat, out of ten heat responsive units three fired on the first heat run. In two of these instances the units were found early in an experiment before the skin had been subjected to noxious stimulation.

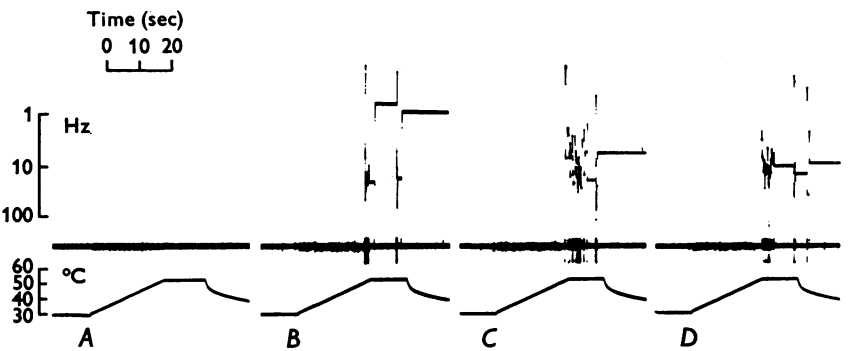

Fig. 7. Heat responses of a cat HTM. The first three heat stimuli (to 48 or 52° C) are not shown. These, and the 4th stimulus (*A*) produced no firing. The fifth to eighth stimuli (*B–D*) produced rapid bursts of firing. All stimuli shown were to 52° C with a 10 sec hold. The three traces are as in Fig. 6.

Typical heat responses are illustrated for a rabbit HTM unit in Fig. 6 and for a cat unit in Fig. 7. The rabbit unit was twice heated to 50° C with no response (Fig. 6*A*, *B*). The third heat run was to 55° C and the unit fired 47 times late in the stimulus, as the skin temperature was falling. The appearance of firing during the cooling phase of a stimulus was a common prelude to more obviously heat related firing and Fig. 6*D* shows that the next heat trial on this unit produced vigorous firing during the heating phase of the stimulus. The responses of HTMs during cooling are therefore probably related to some effect of the heating which develops more rapidly on subsequent stimulation. A number of HTMs have been tested with rapid skin cooling produced by spraying ethyl chloride on to the skin, and none fired.

Sensitization is illustrated dramatically by comparing Fig. 6*A* and *B* with Fig. 6*D*. The stimuli were identical in each case, the peak temperature being 50° C, but whereas the unit failed to respond in the first two

trials it fired 196 spikes during the 4th trial. Subsequent responses to further 50° C stimuli were less vigorous, but still large, until after the 9th stimulus, when the skin temperature was held at 55° C for 30 sec. After this stimulus the unit no longer responded to thermal or mechanical stimulation.

The responses of the cat HTM shown in Fig. 7 followed a similar course. The stimulus shown in Fig. 7*A* is the 4th, the unit having previously been heated twice to 48° C and once to 52° C. The unit did not fire to the 4th stimulus, but did fire to the next, identical, stimulus which is shown in Fig. 7*B*. The firing pattern of this unit was very irregular, with short bursts of up to 100 Hz following pauses lasting some seconds. Similar erratic firing was observed in a number of units. Fig. 7 once again illustrates heat sensitization; the sequence of identical stimuli produce 0, then 33, then 49 spikes. This unit fired slightly less vigorously to the fourth stimulus (42 times). When stimuli are repeated every 3 min such fatigue is perhaps to be expected. This unit was, however, still responding at the 11th heat run to 52° C. In three experiments non-destructive heating tests were repeated over a period of 45 min. Sensitization to heat was observed to continue throughout this period and showed no signs of disappearing. However, a small number of rabbit units only responded 2 or 3 times to heat stimulation, the heat responses ceasing before response to mechanical stimulation disappeared.

HTMs were never spontaneously active at the beginning of an experiment, but some developed background discharge after repeated stimulation. This was often, but not invariably, associated with the development of heat sensitivity. The background firing was irregular, consisting of bursts of spikes followed by pauses of several seconds. Average frequencies rarely exceed 1 Hz.

When a heat sensitized unit was heated for many seconds, or when the skin temperature was raised to 55 or 60° C, firing usually stopped abruptly well before the end of the stimulation. The exact pattern of this 'shutting off' was variable from run to run and from unit to unit.

Mechanical responses during heating. Two mechanical tests were given to HTMs at 1 min intervals between heat runs. There was no consistent increase in mechanical responsiveness associated with heat sensitization. There was usually an early increase in responses to the mechanical test stimuli at the start of the heat trials apparently unrelated to whether there was a heat response or not. There was always an eventual decline in mechanical responsiveness as heating progressed. The problem of small skin movements affecting the results of repeated mechanical stimulation was mentioned above and may also have been a confusing factor here.

Inactivation following prolonged heating. Both heat sensitive and heat

insensitive HTMs eventually became unresponsive to thermal and mechanical stimulation if heated repeatedly to high temperatures. The amount of heating needed to inactivate units varied, but lay within certain limits. Heating up to 50 or 55° C never produced inactivation. However, holding the skin temperature at 55° C for 30 sec often did. Those that survived a hold at 55° C were almost all destroyed by holding the skin at 60° C for 30 or 60 sec. When part of the receptive field had been protected from heating by aluminium foil, the spots underneath it responded normally to mechanical stimulation even though other spots were inactivated.

DISCUSSION

The striking feature of the heat responses of HTMs is the way they increase with successive stimuli. Sensitization of heat responses with repeated stimulation has previously been described for polymodal C-fibre units (Bessou & Perl, 1969) and for cold units (Dubner, Sumino & Starkman, 1974). The sensitization is more dramatic for the HTMs because they will not usually respond at all to the first heat trial (at least, not when the stimulus is applied to 1° C/sec).

The sensitization of HTMs was, like that of polymodal C afferents, long-lasting. However, there did appear to be limits to the extent at which HTMs would fire to heat. Repeated stimulation led to fatigue and prolonged or very intense stimulation led to cessation of firing. If stimulation were strong enough the cessation of firing was permanent and the unit ceased firing to thermal and mechanical stimulation. Low threshold mechanoreceptor units were also found to be inactivated by similar temperatures and durations, as was reported by Beck *et al.* (1974). The levels of heating required to produce apparently irreversible inactivation (55° C for 30 sec was about the average) are similar to the level of heating which was shown by Moritz & Henriques (1947) to lead to irreversible changes in the structure of the skin of pigs. In our experiments repeated heating to 50–55° C produced easily visible oedema, and sometimes obvious reddening, in the heated area.

The difference between the levels of heating required to produce heat sensitization of HTMs and the level that produced inactivation was not great. It is possible therefore that we inactivated some units before they could develop heat responses by increasing succeeding stimuli in 5° C steps. For this reason it is difficult to be certain about the proportion of HTMs that would become heat sensitive under the correct conditions. It certainly seems probable that it would be nearly all the cat units and more than half of the rabbit units; possibly all HTMs have the potential to develop heat sensitivity. Certainly, measurements of other properties show

that the HTMs form a single population and there was no tendency for heat sensitive units to differ from non-heat sensitive ones in receptive field dimensions, conduction velocity or mechanical sensitivity.

The ability of many HTMs to develop heat sensitivity after repeated heating helps to explain the disagreement between the two previous studies on cat HTMs. Burgess & Perl (1967), who used fairly brief heat tests in skin which had not previously been heated, failed to find heat responsive HTMs. Beck *et al.* (1974) found many heat responsive HTMs, but they used a 50° C, 10 sec duration, search stimulus. The skin in their experiments would therefore soon have received enough heatings to sensitize many HTM units.

There are a number of reports of heat sensitive afferent units with small myelinated axons in primates (Iggo & Ogawa, 1971; Dubner *et al.* 1974; Georgopoulos, 1976). Most of these units had receptive fields that consisted of one small zone, not many separate points. From limb hairy skin, these units had very slowly-conducting axons and these receptors may be more like the polymodal nociceptors with unmyelinated axons, which also have similar small receptive fields. This would be like the situation with cold fibres from the hairy skin of the limb which are all unmyelinated in cat, but are partly myelinated in primate (Hensel, 1973).

In view of the very few HTMs that respond to the first heat stimulus, it seems unlikely that these units play any significant role in signalling the first pain that follows immediately after a noxious heat stimulus to the skin. Studies of heat sensitive HTMs in primate face (Dubner *et al.* 1974) and hand (Georgopoulos, 1976) have also concluded that these units play little part in signalling first heat pain. However, the situation in previously heated skin is clearly quite different. Although, as pointed out by Beck *et al.* (1974), the discharge of HTMs can be very erratic, they are not completely unrelated to skin temperature. It is known that in man the skin in a region of heat damage becomes hyperalgesic (Lewis, 1942) and it is possible that the change in sensitivity of HTMs may play a part in producing such effects.

Nevertheless, the principle biological role of HTMs seems likely to be the rapid signalling of information about contact with sharp objects, since this is the type of stimulus which excites them best under most circumstances. In this context it is interesting that the rabbit HTMs on the foot have particularly small fields. Since the rabbit walks on this part of its foot the probability of an adequate stimulus being received there must be enhanced and so a greater spatial resolution in the afferent pathway might be useful. In contrast, the cat, which walks only on the specialized pad, has the same large fields on the proximal part of the foot as it does on the lower leg.

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