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RESPONSES OF CAT CORNEAL SENSORY RECEPTORS TO MECHANICAL AND THERMAL STIMULATION

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SUMMARY

1. The afferent responses evoked by mechanical and thermal stimulation of the cat cornea were recorded extracellularly from strands of long and mixed ciliary nerves under deep anaesthesia. 94 % of the units studied (n = 53) responded consistently to both stimuli.

2. Conduction velocities, measured by electrical stimulation of the receptive field, corresponded to the lower range of the A-delta fibre group (average = 5·4 m/sec). Receptive fields covered approximately a quadrant of the corneal surface and showed continuous sensitivity and overlapping. Units were silent in the absence of stimulation but an ongoing activity was commonly present after repeated mechanical and thermal stimulation.

3. Mechanical responses were evoked at low thresholds and consisted of a dynamic and static response that paralleled the amplitude of the stimulus. The pattern of the discharge was irregular and fatigue was easily developed by repeated stimulation.

4. Thresholds to heating were above 38 °C and the response increased monotonically with the temperature over the range from threshold to 50 °C. The heat response could be sensitized by repeated long suprathreshold stimulation while variable changes in the response were induced by briefer stimuli. Also depression was observed in some circumstances. A weak response to cooling was present in 50 % of the units tested.

5. Damaging mechanical stimulation or the application of a strong acid solution evoked a vigorous response followed by an after discharge that persisted for hours.

6. The relation of these receptors to other polymodal nociceptors and corneal sensation is considered.

INTRODUCTION

The idea that a definite population of thin-fibre endings is involved in the transduction of painful stimuli has been supported in recent years by the description of several A-delta and C afferents in somatic structures that respond differentially to noxious stimulation (Burgess & Perl, 1973). These receptors have some functional properties such as polymodality and sensitization (Bessou & Perl, 1969; Fitzgerald & Lynn, 1977; Kumazawa & Mizumura, 1977) that point to further physiological differences between the so-called nociceptors and the low-threshold receptors.

Recent psychophysical experiments on corneal sensibility have confirmed the view

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that nocifensive reflexes, irritation and pain are the only reactions to thermal stimulation of the human cornea (Kenshalo, 1960; Beuerman & Tanelian, 1979). This is also the case for mechanical stimulation except for periliminal intensities (Lele & Weddel, 1956; Schirmer, 1963). These observations suggest the corneal endings could share some functional properties with other somatic nociceptors. However, electrophysiological data on corneal sensory receptors are scarce and no quantitative description of the response has been attempted (Tower, 1940; Lele & Weddell, 1959; Mark & Maurice, 1977).

The present experiment was aimed at establishing the functional properties of corneal sensory receptors on a more quantitative basis, and to see whether they could be categorized as nociceptors or not. Special attention has been paid to determine the threshold and range of the response to mechanical and thermal stimuli and to explore the changes in sensitivity induced by repeated stimulation. Some preliminary results have been reported elsewhere (Giraldez, Geijo & Belmonte, 1979).

METHODS

Experiments were performed on twenty-three adult cats anaesthetized with an initial dose of sodium pentobarbitone (40 mg/kg, I.P.) supplemented as required, to maintain a deep arreflexic state, by I.V. infusion of dilute anaesthetic (10 mg/ml.). Animals were spontaneously breathing; blood pressure and rectal temperature were continuously monitored, the last being maintained at 36–38 °C by external heating.

The head was fixed in a stereotaxic frame and the superior and lateral wall of the orbital cavity removed. After resection of the extrinsic muscles of the eye, ciliary nerves were exposed, carefully dissected under a binocular microscope and placed on Ag-AgCl electrodes. The nerve was covered with warm mineral oil and the dissection continued until a single identifiable unit was evoked by natural stimulation. Most of the recordings were made from mixed ciliary nerves where fewer active corneal units were evoked and more easily isolated. The corneal surface was kept moist by saline solution flowing from a reservoir. Impulse discharges were recorded with conventional electrophysiological equipment consisting of a.c. amplifier with modifiable filters to maximise the signal to noise ratio (usual bandpass 100–1500 Hz), oscilloscope and loud-speaker.

Conduction velocities were calculated from the delay of the evoked response to suprathreshold electric shocks (0·1–0·5 msec, 0·5–3 mA), applied with a pair of silver electrodes on the receptive area, and the conduction distance measured post-mortem. In some cases a double recording technique was also employed (Fidone & Sato, 1969).

Mechanical stimulation of the cornea was carried out with a Cochet-Bonnet aesthesiometer provided with a no. 12 nylon filament, (0·12 mm diameter, 0·0113 mm^2). The length of the filament can be adjusted and the exerted force is read directly on a scale calibrated in mg. A moving coil transducer (Ling Dynamic Systems 100–101 vibrator) provided with a 0·8 mm diameter probe and monitored by a differential transformer (Hewlett-Packard 7DCDT-050) was used to apply square wave and trapezoidal indentations. Final displacements rarely exceeded 250 μm, pulse durations ranged from 1 to 5 sec and indentation velocities were varied between 2 and 20 μm/sec.

Thermal sensitivity was tested with an electronically controlled thermode (22 mm^2 surface area), consisting of a Peltier module monitored by a thermocouple buried in the probe, centred on the receptive field. The system allowed heating or cooling in a controlled manner between 0 and 50 °C, and it could be driven either manually or by an external signal generator. Three different stimulus patterns were employed in this study: (i) stepwise heating from an adapting 35 °C temperature to final values of 46–50 °C, each step lasting from 15 sec and the rate of change from one temperature to the next being 1 °C/sec; (ii) Heating ramps at a constant rate of 0·5 °C/sec, starting at 35 °C and reaching final temperatures of 46–50 °C; (iii) Heat pulses of 10 and 15 °C above the adapting temperature of 35 °C, lasting for 30 sec and with rates of 0·5 and 2 °C/sec. Each stimulus was ended by active cooling. Sensitivity to cold was also tested by active cooling under 35 °C in a way similar to heating.

Damage of the receptive area was performed by pinching or scratching the cornea with a needle; in some cases a cotton ball soaked with a strong acid solution (0·1 N-HCl) was applied on the corneal surface.

Impulse discharges together with the output of the mechano-electric transducer or the thermocouple, and time-reference signals were recorded on FM magnetic tape for subsequent analysis off line. Interspike intervals, average impulses per second and response latencies were measured with an Intertechnique Didac-4000 computer. Peristimulus time histograms and instantaneous frequency *vs.* time plots were constructed with the numerical data.

The experimental protocol was as follows: initial identification of the units was made by mechanical stimulation of the cornea, sliding a wet fine brush on the corneal surface. The receptive field was then mapped with the brush and after a pause of at least 3 min, force threshold was estimated with the aesthesiometer, starting from the lowest intesity (11 mg) and increasing the force exerted until a consistent response was evoked. The procedure was repeated after 1–3 min intervals. When the mechanical response was further analysed the electromechanical transducer was employed with the probe centred on the receptive field. Indentation thresholds were estimated by applying square wave pulses of ascending amplitudes as described in force thresholds. Then a new series of square wave or trapezoidal pulses, spaced by 3 min, were carried out. In two thirds of the recorded units the preceding step was omitted and only the threshold, receptive field and the inspection of the evoked discharge at one or two suprathreshold stimulations was taken as a description of the mechanical sensitivity of the fibre. This was to avoid excessive mechanical manipulation prior to the examination of the thermal response. The thermode was then placed on the receptive field and held at 35 °C for 3 min. Most of the units were first tested to heat with any of the stimulus patterns described above except in some cases in which cooling was the initial step. After thermal stimulation units were tested to mechanical damage and to strong acid solutions. Finally, conduction latencies were measured by electrical stimulation of the receptive field.

RESULTS

General

The following description is based on observations on sixty-six mechano-sensitive corneal units isolated from long and mixed ciliary nerves. Fifty-three units were tested to heat and a consistent response, above 38 °C, was evoked in forty-two of them at the first trial. Nine units responded with a very high threshold (50 °C) or only after repeated exposure to heating and the remaining two were completely unresponsive. Therefore, 94 % of the fibres tested responded to both mechanical and heat stimulation. Since units were identified by their mechanical response, no information could be obtained from this experiment about the existence of a pure thermal-sensitive fibre population.

Conduction velocities of thirty-six corneal units were measured by electrical stimulation of the receptive field. The average conduction velocity was 5·3 m/sec (range = 2·4–20 m/sec), corresponding to thin myelinated fibres in the lower range of the A-delta group. Somewhat higher values (above 10 m/sec up to 24 m/sec) were obtained when estimated in the nerve trunk by simultaneous recording in two points of the nerve (Fidone & Sato, 1969) or when the electrical stimulation was delivered on the limbus. Lower conduction velocities for the intracorneal path of the axon could account for these discrepancies.

In accordance with previous reports (Tower, 1940; Lele & Weddell, 1959) receptive fields were round or oval, showing continuous sensitivity and considerable overlapping. Each fibre supplied approximately a quadrant of the cornea, the corresponding zone of the limbus and a small fringe of the adjacent conjunctiva. Only 30 % of the receptive fields were centrally located without any limbal or conjunctival sensitivity.

Units were silent at the beginning of the recordings and background activity was present only after mechanical or thermal stimulation (see below).

Response to mechanical stimulation

Force thresholds, explored with the Cochet-Bonnet aesthesiometer (see Methods) ranged between 11 and 100 mg, with an average of 43·8 mg ($n = 55$). 30 % of the units were recruited with intensities lower than 30 mg and five of them probably had thresholds under the resolution of the instrument as judged by the very consistent response to the lowest intensity tested (11 mg). Values of indentation thresholds for square-wave pulses ranged from 20 to 100 μm (average 46·7 μm, $n = 17$). No differences in thresholds were found among central and peripheral receptive fields. Moving stimuli, like the sliding of the nylon filament on the receptive area, were usually more effective in evoking a response than those normally applied, as previously reported (Mosso & Kruger, 1973).

The response to a square wave indentation of the receptive field usually consisted in a brief phasic discharge at threshold. Higher intensities evoked an initial dynamic response followed by a more sustained irregular discharge, both being proportional to the intensity of the stimulus (Fig. 1*A*). The number of impulses evoked varied largely among different units. Instantaneous frequencies of about 100–120 impulses/sec, sustained for no longer than one interval, were reached at intensities of 250 μm and 200 mg. Further examination of five units using trapezoidal stimulation showed that the response at a given intensity was related to the indentation velocity as shown in Fig. 1*B*. Although the frequency of the discharge during the change of amplitude increased with indentation velocity, post-stimulus time histograms revealed an amplitude-locked discharge with no change in the threshold or the number of spikes evoked.

The most striking feature of the mechanical response was the easily developed fatigue as a consequence of repeated stimulation (Fig. 1*C*). Stimulus presentations at 1–30 sec intervals led to a gradual reduction of the number of spikes evoked during both the dynamic and the static response. The response in one part of the receptive field could be inactivated while an adjacent place in the receptive field of the same unit was still responsive. Although no attempt was made to characterize the recovery, after 3 min from the end of a single pulse the response was always recovered.

An after-discharge usually followed stimulations above 150 μm and after repeated mechanical manipulation a background activity of about 0·1–0·5 impulses/sec developed in most cases.

Responses to heating

Stepwise Heating

The response to stepwise increments in temperature was studied in twenty-six units. Twenty-one of them responded by increasing the firing rate on increasing temperature as shown in Fig. 2*A*. The threshold of the response ranged between 38 and 46 °C with an average of 41·5 °C. The remaining five units did not respond or gave an erratic discharge at 50 °C, changing to a more consistent response in the following runs (see below). No clear relationship was found between mechanical and heat thresholds in the present study. The pattern of the discharge was irregular and

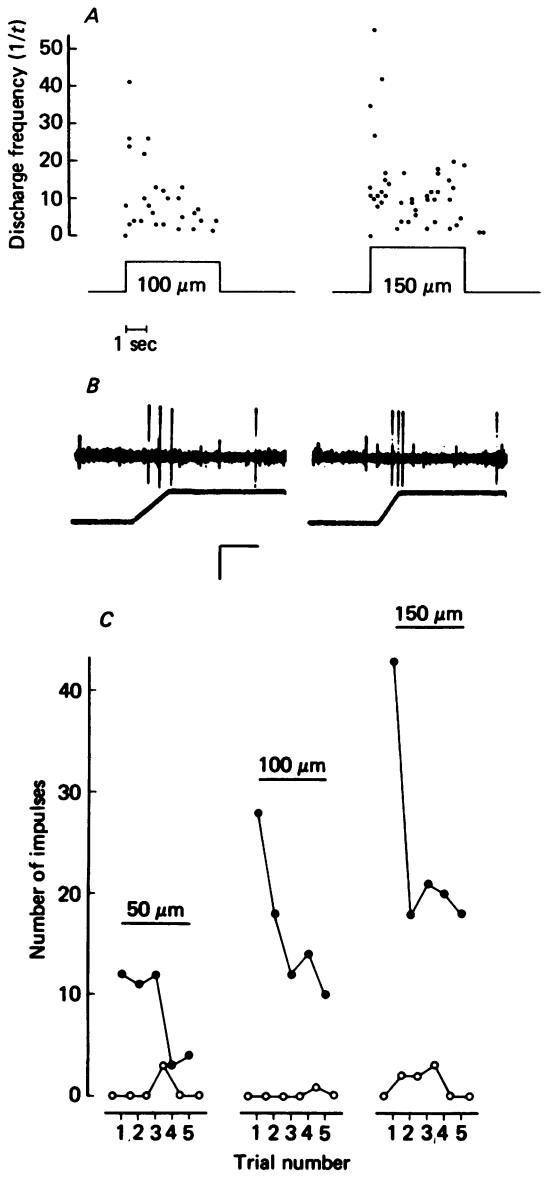

Fig. 1. Mechanical response of corneal receptors. *A*, responses to square-wave indentations of different amplitudes. Instantaneous frequency (the reciprocal of the interval between each impulse and the preceding one) is plotted *vs.* time of occurrence in the upper trace. Lower trace shows the displacement of the electromechanical stimulator at the intensities indicated below each deflexion. *B*, response of another corneal unit to different indentation rates. The upper trace shows the recorded activity and the displacement transducer output is shown in the lower. Vertical calibration = 200 μm, horizontal calibration = 20 msec. *C*, fatigue of the mechanical response. The number of impulses evoked per stimulus (●) is plotted *vs.* the stimulus order for three different series of square-wave indentations, at the amplitudes indicated by each bar. Interstimulus interval was 5 sec for the five successive pulses at a given amplitude, and 3 min were left between two series at different amplitudes. Pulse duration was 5 sec. The number of impulses evoked during the interstimulus period (○) is also plotted in a similar way. Data were obtained from the same unit as in *A*.

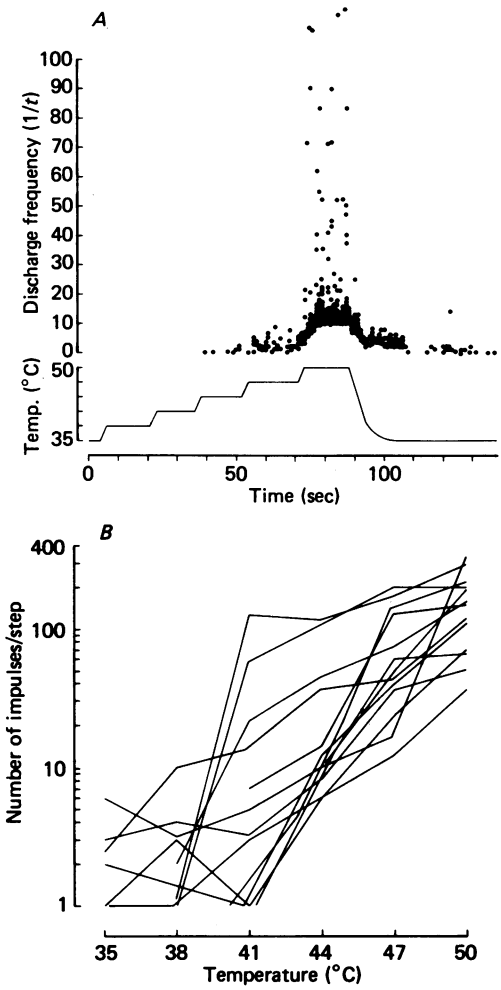

Fig. 2. Response of corneal receptors to stepwise heating. *A*, the instantaneous frequency of the discharge evoked in a corneal unit (upper trace) and the stimulus temperatue (lower trace) are plotted *vs.* time, in a way similar to Fig. 1 *A*. The mechanical threshold of this unit was 27 mg and its conduction velocity 4·3 m/sec. *B*, stimulus–response relations for thirteen corneal units stimulated with stepwise heating as shown in *A*. The number of impulses evoked during each 15 sec step is plotted *vs.* the temperature. Note the logarithmic scale in the ordinates.

the temporal course of the response to each temperature step varied among the different units. In spite of this variability in the pattern of the response, the total number of spikes evoked increased in a regular manner with increasing temperatures. Stimulus–response relations obtained from thirteen units stimulated up to 50 °C are presented in Fig. 2 *B*. The number of evoked spikes increased monotonically with the temperature over the range from threshold to final temperatures of 50 °C. The responses fitted reasonably well to exponential functions (correlation coefficients ranging from 0·80 to 0·99 for at least four data plotted). Peak rates of firing also

followed a similar relation with temperature, reaching values of 17·1 ± 11·4 impulses/sec (mean ± S.D., $n = 17$) at 50 °C. Peak instantaneous frequency was roughly correlated with stimulus intensity. Interval durations corresponding to frequencies of 100–150 impulses/sec, rarely sustained for longer than one interval, were observed at final temperatures of 47–50 °C. Returning the thermode temperature to 35 °C, at the end of the stepwise heating, silenced the response in a few seconds and then an ongoing background discharge was elicited (Fig. 2*A*). Spontaneous activity ranging from 0·2 to 2 impulses/sec was observed in the following three minutes in fourteen units that were either silent or discharging at a frequency under 0·1 impulses/sec before heating.

The repetition of the staircase heating after a 3 min interval led to the sensitization of the response, increasing the number of spikes evoked at a given temperature and lowering the threshold (Fig. 3*A*). The number of impulses was increased 2 or 3-fold at 41, 44 and 47 °C in eight out of twelve units in which the first heating reached a final temperature of 50 °C (Fig. 3*B*), no apparent change being found in the remaining four. Although threshold identification was often hampered by the development of background activity after the first trial, the discharge during the second heating usually began to increase above control (35 °C) levels at one or two steps before it did in the first run. This corresponds to a 3–6 °C lowering of the threshold when compared to the previous heating cycle. When a third cycle was performed, after another 3 min interval, the stimulus-response relation obtained was similar to that of the second trial in the range from 38 to 47 °C. However, a clear depression of the response was observed at 50 °C; a mixed sensitization-depression effect similar to that described in some somatic nociceptors by other authors (Croze, Duclaux & Kenshalo, 1976) was apparent. Four out of the five units quoted above that responded only at 50 °C during the first trial, began to respond at 41–44 °C after a second or a third stimulation showing monotonically increasing stimulus–response relations. The background activity developed after the first heating tended to increase slightly with the following stimulations. No change was observed in the force threshold in a few cases in which it was carefully measured after sensitization of the heat response.

Ramp stimulation

The response to heating ramps (0·5 °C/sec) from 35 °C up to 50 °C was studied in nine units (Fig. 4). Thresholds for the first response ranged between 37·5 and 47 °C (42·9 ± 2·7, mean ± S.D.). Above the threshold a sustained discharge was evoked and the peak number of impulses evoked per second (15·5 ± 6·5 impulses/sec, mean ± S.D., $n = 9$) was consistently observed at final temperatures of 49–50 °C. However, the point to point correlation between firing rate and temperature was poorer than in stepwise experiments. The pattern of the discharge and the temporal profile were irregular in most of the units tested as shown in Fig. 4. A poor reproducibility of the response was observed with repetition of the stimulus. The total number of impulses evoked per stimulus tended to be lower when 50 °C ramps were repeated at 3 min intervals, except in one case in which the response became sensitized.

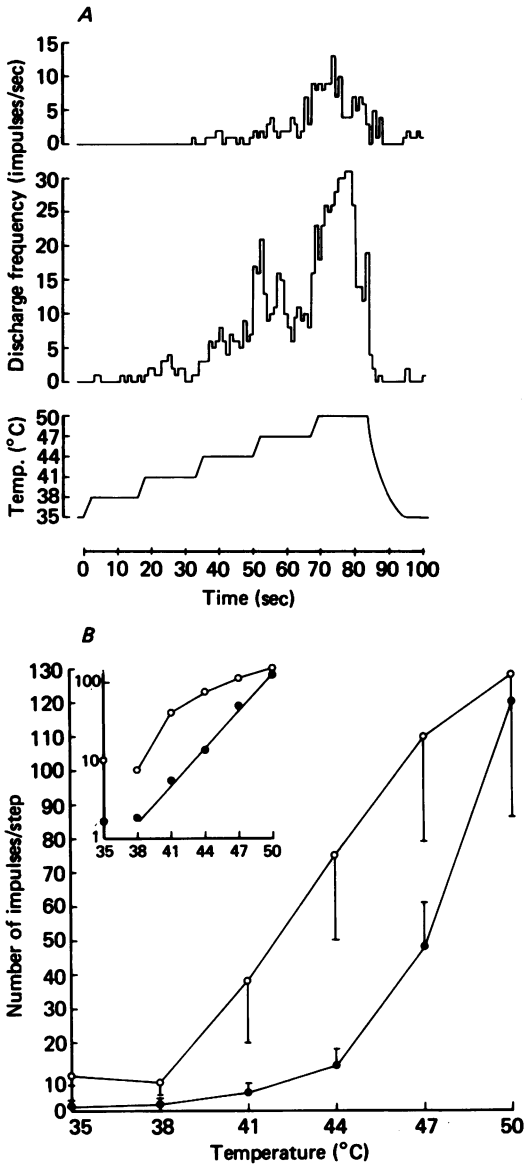

Fig. 3. Sensitization of the heat response of corneal receptors. *A*, peristimulus histograms of a corneal unit showing the first (upper) and second (lower) response to two identical stepwise heatings separated by 3 min. Each bar indicates the number of impulses evoked per second and the lower trace shows the stimulus waveform. *B*, mean stimulus response relation of eight corneal units in response to the first (●) and the second (○) stepwise heating. Each point represents the mean number of impulses evoked at the temperature indicated in the abscissa. The bars indicate S.E. of mean. The increase of the response was significant ($P \leqslant 0{\cdot}05$, t paired test) at 41, 44 and 47 °C. The inset shows the same data plotted in log-linear co-ordinates.

Heat pulses

Eighteen corneal units were stimulated with 30 sec duration heat pulses of 10–15 °C above a constant adapting temperature of 35 °C. In order to study the possibility of sensitizing the response by means of an intense and prolonged exposure to the stimulus, nine of these units were successively tested with heat pulses of 45, 50 and again 45 °C, separated by 30 sec intervals. All units tested in this way showed a clear enhancement of the response to the second 45 °C stimulation (Fig. 5). The average

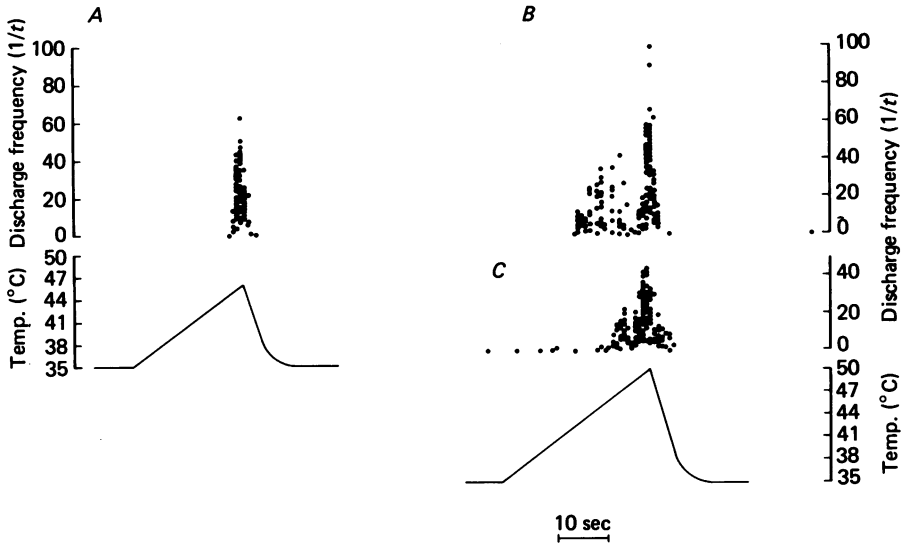

Fig. 4. Response of a corneal unit to successive heating ramps. Graphs were constructed as in Figs. 1*A* and 2*A*. The first stimulus (*A*) was stopped at 46 °C while the following (*B*, *C*) were continued to 50 °C. Interstimulus interval was of 3 min.

number of evoked impulses increased from 20·5 for the first 45 °C stimulation, to 193·0 for the second. The peak rate of the discharge also rose from 3·4 to 16·0 impulses/sec. Two units did not respond at all to the first 45 °C pulse but became responsive after sensitized by the 50 °C pulse. In two units (one shown in Fig. 5*B*) stimulated with further 45 °C pulses, the response was still enhanced within the following 3 min after the 50 °C pulse. In four units the threshold was 1–3 °C lower after the sensitizing pulse.

Because of the confounding interference of sensitization it was not possible to study whether the response was sensitive to the heating rate. However, stimuli delivered at 2 °C/sec evoked a more pronounced dynamic response than those in which the rate of change of temperature was slower (0·5 °C/sec) while the thresholds of the responses fell in the same range for both (39–47 °C).

Response to cooling

Fifteen units were tested to cooling under 35 °C. A slight but significant ($P \leqslant 0{\cdot}05$, paired t test) increase of the spontaneous activity from $0{\cdot}1 \pm 0{\cdot}1$ to $0{\cdot}4 \pm 0{\cdot}2$ impulses/sec (mean $\pm$ S.D.) was observed in eight units when the thermode temperature was changed from 35 to 25–30 °C. This change was not further related to the temperature

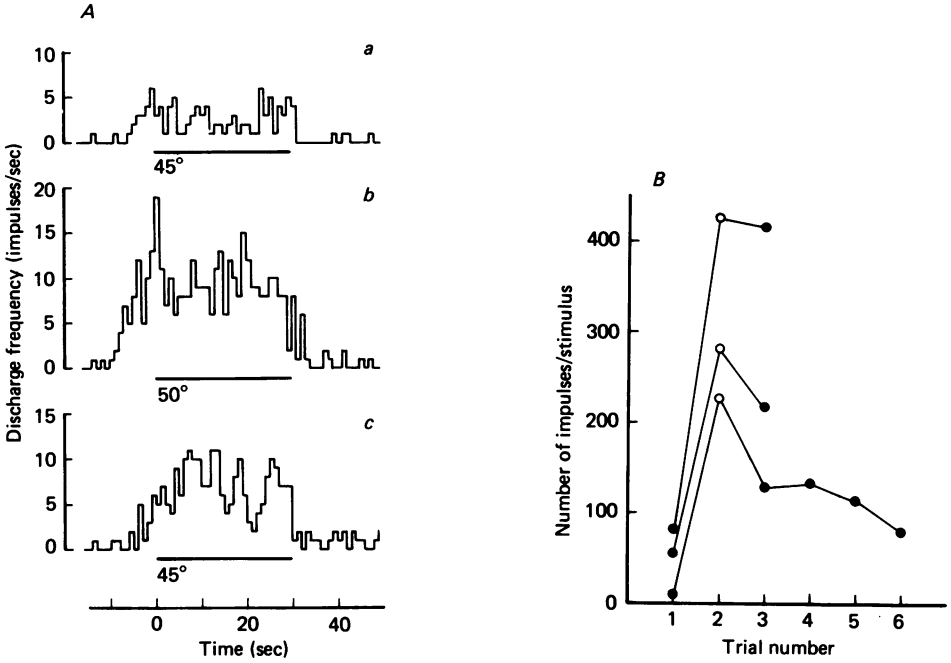

Fig. 5. Sensitization of corneal receptors by heat pulses. *A*, peristimulus histograms of a corneal unit in response to three successive heat pulses of 45 °C (*a*), 50 °C (*b*) and again 45 °C (*c*). The bar under each histogram shows the stimulation period at the steady temperature indicated below. Adapting temperature was 35 °C in all three stimulations, rising rates were 0·5 °C/sec and the interstimulus interval 30 sec. *B*, responses evoked in three different units stimulated as in *A* are plotted as the number of impulses evoked per pulse against the stimulus order. The response to the second trial (○) corresponds to a 50 °C stimulation while the rest (●) to 45 °C. Each line is for a different unit; one of them was further stimulated after the third trial at 30 sec intervals.

down to 5 °C and usually all spontaneous activity was silenced under 20 °C, returning when 25–30 °C was regained. The situation was not modified by the sensitization of the heat response.

Response to mechanical damage

The response to overtly damaging stimulation of the cornea was studied in thirty-five mechano-heat sensitive units. Scratching the receptive area elicited a high frequency discharge (100 impulses/sec) with interval durations equivalent to 250–300 impulses/sec, followed by a long lasting after-discharge (Fig. 6*A*). Firing rates during the after-discharge reached values of up to 15 impulses/sec, with irregular bursting periods in which the instantaneous frequency reached 50–70 impulses/sec. Following damage, threshold and near threshold responses were depressed but often a renewal of the ongoing activity was produced by mild periliminal stimulation. After 1 min from the end of the stimulation the frequency of the background activity tended to decrease but it remained unabated until the end of the experiment (1–5 h).

In the cases in which a strong acid solution was applied on the cornea, similar responses were observed (Fig. 6*B*, lower record).

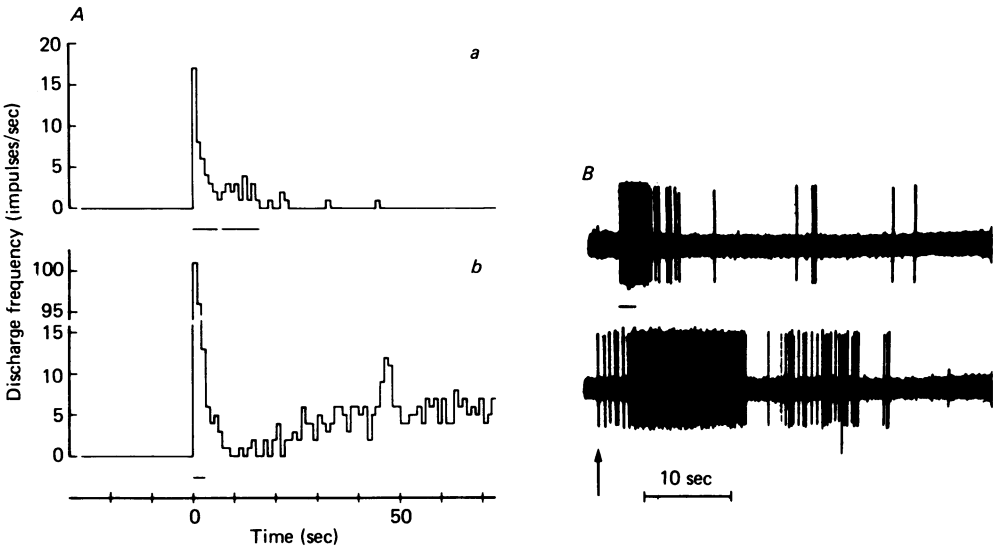

Fig. 6. Responses of corneal receptors to damaging stimuli. *A*, peristimulus histograms of a corneal unit (same as in Fig. 1 *A*, *C*) in response to a mild stimulation performed by sliding a fine brush on the receptive field (*a*), and to mechanical injury of the receptive area by scratching it with a needle (*b*). Stimulation periods are indicated by the bars below each histogram. *B*, response of another corneal unit (same as in Fig. 5) to the mechanical damage (upper record) and to the application of a strong acid solution on the receptive field (lower record). The bar in the upper trace indicates the period of stimulation and the arrow in the lower the time at which a cotton soaked with 0·1 N-HCl was applied on the receptive field. Same calibration for both recordings.

DISCUSSION

The present report describes a distinct population of A-delta afferents responding to mechanical and thermal stimulation of the cat cornea. The striking similarities between the functional properties of the corneal receptors and those of polymodal nociceptors, described in other tissues, suggest that both belong to the same receptor category. In addition to being polymodal, as was noted by Lele & Weddell (1959), the corneal receptors reported here have the following characteristics also reported for polymodal nociceptors innervating the skin and deep tissues of several animal species: (i) the mechanical response shows its maximum sensitivity in the noxious range although threshold mechanical stimuli are not necessarily painful. The response consists of a dynamic and a static component with an irregular pattern of discharge (Bessou & Perl, 1969; Kumazawa & Perl, 1977; Kumazawa, & Mizumura, 1977, 1980); (ii) repeated mechanical stimulation commonly develops fatigue and an ongoing background activity (Bessou & Perl, 1969; Georgopoulos, 1976; Kumazawa & Mizumura, 1980); (iii) heat thresholds are above 38 °C and the response is graded above the liminal value with bursts of impulses followed by periods of quiescence (Bessou & Perl, 1969; Kumazawa & Perl, 1977). The maximum sensitivity is in the 45–50 °C range (Iggo, 1959; Bessou & Perl, 1969; Beck, Handwerker & Zimmermann, 1974; Beitel & Dubner, 1976; Handwerker & Neher, 1976; Croze *et al.* 1976); (iv) a

change in responsiveness is induced by noxious heat leading to the sensitization or depression of the response; this is usually accompanied by changes in background activity (Bessou & Perl, 1969; Beck *et al.* 1974; Beitel & Dubner, 1976; Croze *et al.* 1976; Lynn, 1979; Kumazawa & Mizumura, 1977, 1980); (v) a weak sensitivity to cooling is commonly present (Iggo, 1959; Bessou & Perl, 1969; Kumazawa & Mizumura, 1980); (vi) irritant chemicals, such as strong acids, also can evoke a response (Bessou & Perl, 1969).

Polymodal nociceptors innervated by either A-delta or C fibres have been reported in the skin and deep tissues (Iggo & Ogawa, 1971; Georgopoulos, 1976; Dubner, Price, Beitel & Hu, 1977; Kumazawa & Mizumura, 1977, 1980). The conduction velocity of corneal sensory fibres, measured from the delay to the electrical stimulation of the receptive field, corresponds to the lower range of the A-delta fibre group. Although the fibre spectra from the cornea is not known, some evidence suggests that most fibres are thin myelinated (Lele & Weddell, 1959). A slowing down of the conduction velocity at the terminal part of the axon is suggested by our measurements in the nerve trunk and can be expected from the unmyelinated intracorneal parts of the fibres (Ramón y Cajal, 1909; Zander & Weddell, 1951).

Sensitization to heating has been reported in few receptors apart from C-polymodal nociceptors of the skin (Dubner, Sumiro & Wood, 1975; Fitzgerald & Lynn, 1977) and therefore this property constitutes a quite specific taxonomic criterion. Although not fully analysed, the stimulus requirements for sensitization of corneal sensory receptors (long and intense exposure to heating) seem to be close to those of C-polymodal nociceptors (see Campbell, Meyer & Lamotte, 1979). The relation between sensitization and background activity remains obscure though the conditions that lead to both phenomena are similar. As the cornea is devoid of blood supply, it is clear that the induced change in responsiveness is independent of changes in the local blood flow, as recently suggested by Lynn (1979).

Morphologically, these receptors correspond to the free nerve endings distributed in the upper third of the stroma and the superficial epithelium, since those are the only nerve terminations described in the cornea (Ramón y Cajal, 1909; Whitear, 1960). The unitary receptive fields and thresholds reported here are consistent with the pattern of distribution of each nerve fibre and the superficial location of the endings.

Finally, a fair correspondence between the receptor properties and the known psychophysical data can be outlined. Contact thresholds for the sensory response, estimated with the Cochet-Bonnet aesthesiometer or similar instruments, are about 20–30 mg (Schirmer, 1963; Millodot, 1973). A low threshold to pain, a high sensitivity to moving stimuli and the persistence of the sensation outlasting mechanical stimulation are characteristics of the corneal sensation (Lele & Weddell, 1956; Schirmer, 1963). The sensory response to heating changes from neutral to irritating at 38–42 °C and from very irritating to painful at 44–47 °C. Cooling to 30–31 °C also evokes irritation. Neither heating nor cooling evokes a pure thermal sensation if the stimulus is carefully restricted to the cornea (Kenshalo, 1960; Beuerman & Tanelian, 1979). The general properties of the receptors reported here could account for these characteristics of the corneal sensation. Since it can be generally accepted that only unpleasant or painful sensations can be evoked by naturally occurring corneal stimuli,

the idea that the sensation of pain is linked to the activation of nociceptors seems to be reinforced by this experiment.

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