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INPUT–OUTPUT RELATION OF TRANSMISSION THROUGH CUNEATE NUCLEUS

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SUMMARY

1. In decerebrate cats, micro-electrodes were inserted into the cuneate nucleus to stimulate afferent terminals with single shocks of varying intensities. Estimates of the input and output of the nucleus were obtained by integrating antidromic responses in forelimb cutaneous nerves and orthodromic responses in the medial lemniscus.

2. Input–output curves were normally very non-linear, reflecting the high synaptic potency of small inputs. They were fitted readily by power functions, with exponents averaging 0·50.

3. The normal input–output relation rapidly disappeared after interruption of the blood supply. A loss of synaptic efficiency of small inputs was indicated by curves with exponents of $\geqslant 1$; this was associated with a sharp increase in terminal excitability.

4. Within the range of surface temperature 30–40° C, warming made the input–output curves steeper but reduced terminal excitability, whereas cooling had the opposite effect. The efficiency of transmission was thus inversely correlated with terminal excitability.

5. The non-linear shape of cuneate input–output curves is probably not determined by inhibitory control, since picrotoxin depressed rather than enhanced outputs.

6. On the other hand, pentobarbitone made the input–output curves markedly steeper and tended to lower terminal excitability.

INTRODUCTION

Since the pioneer experiments of Therman (1941), there have been many studies of synaptic transmission through the dorsal column nuclei (e.g. Amassian & de Vito, 1957; Andersen, Eccles, Oshima & Schmidt, 1964*a*; Carli, Diete-Spiff & Pompeiano, 1967; Andersen, Gjerstad & Pasztor, 1972*a*, *b*). However, there is little information about the global

input–output relations at these nuclei, and the mechanisms that influence the efficiency of transmission.

It is generally believed that the state of polarization of presynaptic terminals is an important determinant of the amount of transmitter released by active terminals (Eccles, 1964). Although some observations on dorsal column nuclei are consistent with this idea – for example, the good correlation between depolarization and increased excitability of primary afferents on the one hand, and depression of transmission on the other (Andersen, Eccles, Schmidt & Yokota, 1964*b*; Cesa-Bianchi, Mancia & Sotgiu, 1968; Andersen, Etholm & Gordon, 1970) – others appear to be contrary. Thus, according to Andersen *et al.* (1972*a*, *b*), the depression of transmission caused by local cooling of the cuneate nucleus is associated with a *reduced* excitability of afferent terminals.

In an earlier paper (Morris, 1971), a description was given of a technique of measuring transmission through the cuneate nucleus, combining direct stimulation of nerve terminals in the cuneate nucleus with recording of the antidromic volley in peripheral nerves and the orthodromic volley in the medial lemniscus. These responses provide respectively estimates of the neural input and output of the nucleus. The efficiency of this technique has been improved in a number of ways, particularly by introducing constant current pulses for stimulation, integrating the area of the responses, and using a computer to standardize the stimulation and analyse quantitatively the input–output relations. We have used this method to study transmission through the cuneate nucleus under a variety of conditions, including different temperatures, and after the administration of a general anaesthetic. Some of the results have been reported briefly (Krnjević & Morris, 1973, 1975*a*).

METHODS

Preparation

All experiments were performed on cats decerebrated under temporary halothane anaesthesia. The brain stem was cut at the mid-collicular level and the whole rostral portion of the brain removed. In nearly half of the experiments, the animal breathed spontaneously and required no further anaesthesia. In the other cases, excessive reactions to nerve stimulation made it necessary to administer small amounts of anaesthetics (N_2O and O_2, and at times 1% halothane) or a paralysing agent (succinylcholine chloride, I.V.). The femoral arterial pressure was monitored routinely and the rectal temperature automatically maintained near 38° C.

Other dissection

The dorsal surface of the medulla and upper end of the spinal cord was exposed by removal of portions of the axis and the atlas, and part of the adjacent occipital bone.

Two forelimb nerves, the median and both branches of the superficial radial, were prepared for stimulation or recording. They were mounted on platinum electrodes, and protected by a thick covering of Vaseline softened with mineral oil.

The dorsal surface of the cuneate region was continually irrigated with physiological saline having the following composition (mM): Na^+ 150, K^+ 2·5, Cl^- 145·5, Ca^{2+} 2·0, Mg^{2+} 1·0, HCO_3^- 12·0 and $H_2PO_4^-$ 1·0. The temperature of this fluid was held at any desired level (usually near 39° C) by a thermostatically controlled heating element surrounding the delivery tubing. When the heating was turned off, the speed of cooling of the fluid depended on the flow rate. It was usually about 2° C/min. Re-heating was more rapid, at a rate of about 10° C/min. To reduce pulsations, a transparent pressor foot was sometimes applied lightly to the medulla, leaving exposed only the site of electrode insertion. A bead thermistor monitored continuously the temperature of the fluid at the surface of the tissue.

Cuneate stimulation

The electrodes were conventional glass micropipettes with relatively large tips (about 5 μm) filled with 1 M-NaCl and 1–2% agar to prevent the escape of fluid. They had a resistance of approximately 1·0 MΩ, and were often combined with two finer-tipped micro-electrodes to record tissue potentials and K^+ levels (cf. Krnjević & Morris, 1974). The tip of the stimulating electrode was about 50 μm behind the other two tips.

The stimuli were rectangular, constant-current pulses, lasting 0·2–1 msec, applied at a rate of about 1/sec. They were of cathodal polarity with respect to a distant Ag:AgCl ground electrode attached to the dorsal cervical musculature. Their intensity could be varied in the range 0–90 μA, either manually, or by a Linc 8 computer. The latter delivered regularly incrementing pulses in groups of 8 or 16 (Fig. 1*D*), each group being repeated every 10–20 sec (cf. Fig. 5*D–E*).

Electrical recording

The antidromic response evoked from one or more of the forelimb nerves was recorded with a differential pre-amplifier. The nerve was crushed between the platinum recording electrodes so as to obtain a monophasic potential. The orthodromic response was recorded differentially from the cut surface of the brain stem, using two platinum ball electrodes (diameter 0·5 mm): one was placed at the 'killed-end' of the medial lemniscus and the other at a site giving a maximal monophasic lemniscal potential and minimal stimulus artifact.

Both types of responses were displayed on an oscilloscope, and recorded from time to time photographically (Figs. 1*A*, 5*A–C*, 8, 9*A–C*). They were also integrated (with respect to time) either by an analogue circuit (Fig. 1*E*) or the Linc 8 computer, the integrals being stored by the computer in digital form on magnetic tape. The computer measured each potential at intervals of 25 or 50 μsec, so every integral was then calculated from at least fifty such estimates. The period of integration was always adjusted to include only the early responses. It was particularly important to exclude the late, dorsal column antidromic reflex, which is not infrequently more substantial than the early, direct response (Figs. 1, 5*A–C*, 8, 9). The characteristic late discharge is readily identified as the antidromic reflex by its disappearance when the frequency of stimulation exceeds 10/sec (Amassian & De Vito, 1957; Andersen *et al.* 1964*a*). An example of the electronic integration of the direct antidromic response is given by the lower traces of Fig. 1*E*. These integrals were also displayed as voltage deflexions on a chart recorder (Figs. 3*D*, 5*D–F*) for regular monitoring of terminal excitability (each voltage level was held for > 50 msec, long enough to be recorded accurately by the ink-writer).

The accuracy and linearity of the integrating function was confirmed by recording the integrals of pulses of known amplitudes and durations. In practice, plots of peak amplitudes (measured from photographic records) against integrals of responses

showed consistently, and over a wide range an excellent linear relationship (Fig. 2*A*) yielding correlation coefficients > 0·97.

Input–output relations of the cuneate nucleus

A number of assumptions are made in deriving input–output relations from our data. First, that the amplitude and particularly the time-integral of the responses is a simple function of the number of active fibres. With monophasic recording, and a relatively homogeneous population of fast-conducting fibres, it is reasonable to assume that the various fibres contribute approximately equal increments to the response. Recording of the area of the response ensures that at least moderate changes in synchronization of firing do not affect the results.

Outputs

Direct stimulation in the cuneate may excite cuneothalamic cells directly (Andersen *et al.* 1964*b*). This leads to the appearance of a distinct, early component in the lemniscal response (α-wave), identified by its short and constant latency, and ability to follow a high frequency of stimulation. This alpha response is practically insignificant when the stimulating micro-electrode is relatively superficial, as in the present experiments (mostly at depths of 0·3–0·6 mm) (cf. Figs. 1, 5, 8, 9).

Thus, the almost pure β-response recorded from the lemniscus must be a good index of the trans-synaptically evoked activity of the cuneate neurones (cf. also Bowsher, 1958; Andersen *et al.* 1972*a*). On the other hand, the antidromic responses recorded from one or even several peripheral nerves can hardly be the total input. The nucleus receives a good number of fibres other than primary afferents (Glees, Livingston & Soler, 1951; Uddenberg, 1968; Dart & Gordon, 1973; Rustioni, 1974), many of which are presumably excited together with the afferents from the forelimb. However, both the electrophysiological (Dart & Gordon, 1973) and the morphological (Rustioni, 1974) evidence suggest that most of these other afferents excite interneurones rather than relay cells. Moreover, it seems not unreasonable to expect that primary and non-primary afferent terminals would undergo comparable changes in excitability under various experimental conditions.

We assume therefore that to a first approximation, the changes in response recorded even in one forelimb nerve are representative of changes in the total input received by the cuneo-thalamic cells. Inadequate sampling of input presumably explains the observation that weak stimulation in certain positions in the nucleus could elicit a clear orthodromic response in the absence of any detectable antidromic response.

Input–output–curve

The experiments normally showed predominantly non-linear input–output relations – whether obtained from response peaks (Figs. 2*B*, 8) or integrals (Figs. 2*C*, 3*A–C*, 4*A–H*, 5*G–I*, 9*D–F* and 10*B*), which usually gave good fits to straight lines on log.–log. graph paper (Fig. 2*D*). The Linc 8 computer was therefore programmed to calculate power functions of the form $y = ax^b$, providing the best fit (with least-squared deviations) to the data obtained in 1–4 cycles of stimulation (total of 16–64 points). These lines of best fit could be displayed (Figs. 4*B–H*, 5*G–I*, 9*D–F* and 10*B*), together with the corresponding estimates of a, b and their estimated errors, as well as the over-all coefficient of correlation (Fig. 4*B*).

In computing these lines, advantage was taken of the fact that, during the experiments, the potentials recorded were suitably attenuated, so that the integrated values of input and output could be displayed on-line, on the Linc oscilloscope

(Fig. 2*C* and other figures). The data points therefore were normalized, taking the values corresponding to the full width and height of the Linc 8 display as equal to 1·0. The equation calculated is therefore more correctly described as $y/y_m = a(x/x_m)^b$, where x_m and y_m are the maximum x and y co-ordinates of the display. Since the variables were thus usually $< 1{\cdot}0$, the exponent b *decreases* as the curves become steeper.

The accuracy of the program was checked by comparing slopes calculated from the integrated values plotted on log.–log. paper against the values of the exponent b (in the equation $y = ax^b$) determined by the computer: six series of points gave mean values for b of 0·550 (S.E. 0·055) and 0·554 (S.E. 0·052) by the two methods respectively, and a coefficient of correlation of 0·941 between the six pairs of corresponding estimates of b.

As a further check, a comparison was made between values of b obtained by plotting against each other on log.–log. paper the peak amplitudes of orthodromic and antidromic responses photographed from the oscilloscope, and those calculated from the integrated responses by the computer (several examples of such plots are given in Fig. 2*D*). Twelve sets of measurements of b (from six separate experiments) gave mean values of 0·611 (S.E. 0·0270) for the oscilloscope data and 0·540 (S.E. 0·0404) for the computer estimates. Clearly, while the two methods of measurement not infrequently agree very closely (cf. Fig. 2*B*), and the mean values differ very little, there is nevertheless a good deal of independent variation (cf. the different log.–log. slopes labelled 2 in Fig. 2*D*, where open points represent peak heights, and closed points integrated values for the same sequence of data). This is presumably due to variations in the shape of the responses, which account for the relatively poor correlation between the pairs of data obtained in these two different ways ($r = 0{\cdot}529$, $n = 12$, $P = 0{\cdot}05$).

RESULTS

A typical series of responses obtained in a non-anaesthetized (decerebrate), spontaneously breathing animal is illustrated in Fig. 1*A*, *B*. They were evoked at a rate of 1/sec by stimulating afferent fibres in the cuneate nucleus with a micro-electrode inserted to a depth of 0·15 mm. The regularly incrementing stimulating pulses are displayed in Fig. 1*D*.

The antidromic responses recorded from the superficial radial nerve are characterized by two main initial peaks followed by the late discharge of the dorsal column relay (Amassian & De Vito, 1957). The latter is usually very pronounced, even at relatively high temperatures (as in the examples of Figs. 5*A* and 8*A*, where the cuneate region was superfused by physiological saline at 40–41° C). Its full magnitude and duration is better seen at slow sweeps (Figs. 1*C*, 8*A*, *B*, 9*A*).

By contrast, the orthodromic, lemniscal response (OD) – whose latency is much briefer, because the conduction distance from the cuneate is relatively short – shows a double early peak, and surprisingly little delayed firing corresponding to the antidromic reflex, at least at temperatures of 38° C or more (cf. Figs. 5*A*, 8*A*, 9*A*).

The most striking feature of the observations is the marked disproportion

between the antidromic and the orthodromic responses evoked by weak shocks, reflected by an initially very steeply rising input–output relation. With stronger shocks, the antidromic responses tend to catch up; so the slope gradually diminishes, to reach a relatively steady value when the responses exceed their half-maximal amplitude. Fig. 2 illustrates typical input–output curves obtained by plotting either peak values of initial responses recorded on film (Fig. 2*B*, open triangles, see also Fig. 8) or the

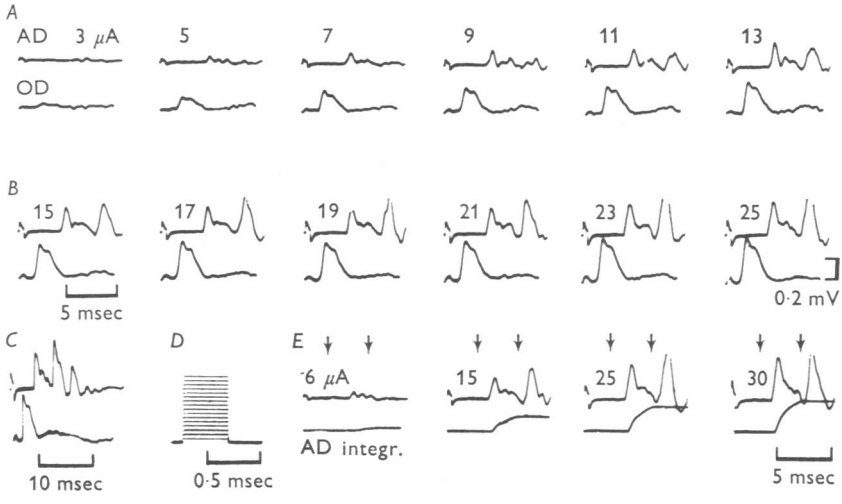

Fig. 1. Typical responses evoked by intracuneate stimulation (at depth of 0·15 mm from dorsal surface), recorded antidromically (AD) from superficial radial nerve and orthodromically (OD) from medial lemniscus at mid-collicular level. Sixteen regularly incrementing voltage pulses from computer (D) were used to deliver constant current pulses through microelectrode, but only twelve pairs of responses are illustrated, the current strength being indicated. Trace *C*, on slow sweep, displays also late peaks of antidromic reflex. Trace *E*: integrated early antidromic responses (period between arrows) are displayed in lower traces; note integration stops before first antidromic reflex peak.

time integrals of the initial response (Fig. 2*B*, black triangles, and Fig. 2*C*; see also Figs. 3–5, 9, 10). As shown by the examples of Fig. 2*C*, successive cycles of stimulation indicate little variation in the input–output relation (compare the single sets of 16 points obtained in one cycle, at left, with the 64 points recorded in four successive cycles, over a period of 1 min, at right).

These patently non-linear relations were usually consistent with power functions ($y = ax^b$), having values varying in fourteen experiments between 0·6 and 1·6 for a, and between 0·3 and 0·8 for b. However, *mean* values proved to be very close to 0·9 for a, and 0·5 for b. This can be seen

from the means in Table 1, calculated from data grouped in three ways: (1) the first control series recorded in fourteen different experiments; (2) nineteen series obtained at different positions and depths in one experiment; and (3) a total of ninety-two separate control series recorded in all fourteen experiments.

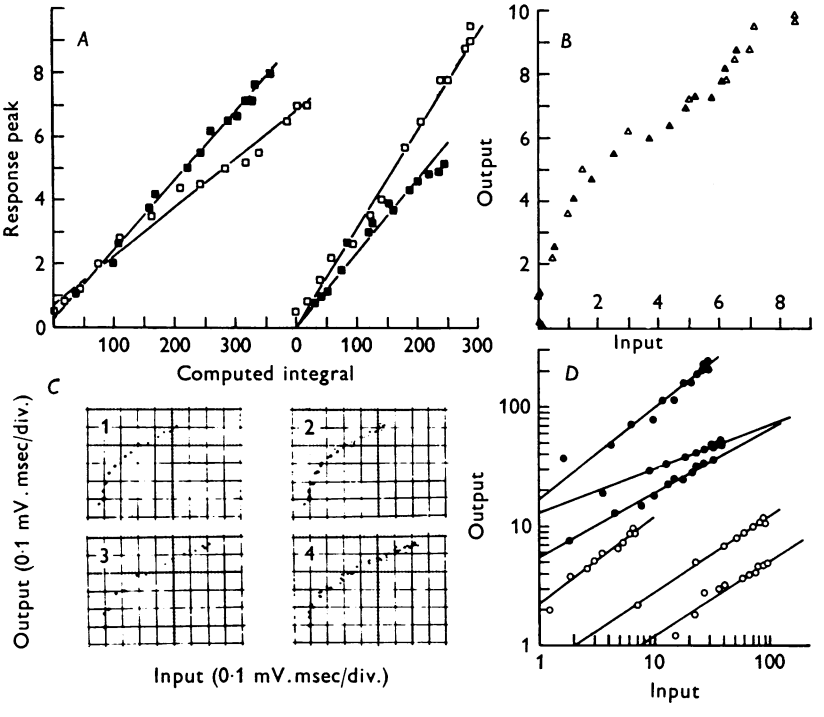

Fig. 2. Comparing responses obtained in different ways.

A: plots of peak amplitude of two sets of early antidromic (open squares) and orthodromic responses (filled squares) against computed time integrals of same responses.

B: plot of antidromic (input) against orthodromic (output) responses, estimated respectively from peak values on oscilloscope traces (open triangles) and integrals calculated by computer (filled triangles.) Scales are arbitrary.

C: input–output curves displayed by Linc 8 computer. Each point represents, on horizontal axis, time integral of early antidromic response, and on vertical axis, time integral of early orthodromic response. (1) Data obtained in one cycle of sixteen regularly incrementing stimulations at 1/sec. (2) Data from four successive such cycles (total of sixty-four stimuli). (3) and (4) a series recorded in another experiment, also showing respectively one cycle and four successive cycles. Note approximate calibration is same for horizontal and vertical axes.

D: plots of antidromic against orthodromic responses on log.–log. graph. Open circles: three separate series of peak amplitudes. Filled circles: corresponding integrated data. Straight lines were fitted by eye.

One can conclude that the average input–output relation estimated by this technique is well represented by the equation $y/y_m = 0{\cdot}9\ (x/x_m)^{0{\cdot}5}$; in other words, the output appears to be proportional to the square root of the input. These data are in agreement with the previous observations showing a non-linear input–output relation at the cuneate nucleus (cf. Fig. 10 in Morris, 1971). However, the analysis of the data in that paper did not sufficiently take into account the origin of the curves, and so led to the conclusion that transmission was linear.

TABLE 1. Mean values of a and b in power functions ($y = ax^b$) providing best-fit for observed input (x)–output (y) relations of cuneate nucleus.

Group 1. Taking first control run from fourteen experiments.

Group 2. Nineteen control runs obtained by stimulation at different depths and positions in one experiment.

Group 3. Ninety-two control runs in all fourteen experiments; for every control run, curve of best fit was calculated for four successive cycles of sixteen stimuli each

	Mean a	S.D.	Mean b	S.D.
Group 1	0·866	0·298	0·474	0·135
Group 2	0·884	0·1759	0·445	0·139
Group 3	0·898	0·2801	0·498	0·1685

Stimulation at different depths

Changes in position of the stimulating micro-electrodes altered the input–output curve in two different ways. First there was a regular tendency for the largest antidromic responses to be evoked relatively superficially, at depths between 0·10 and 0·30 mm from the dorsal surface. This is illustrated in Fig. 3. The lower ink-writer traces record the integrated early antidromic responses evoked at 1/sec by a constant current pulse (initially of three quarters maximal intensity) while the stimulating micro-electrode was inserted into the dorsal column and cuneate nucleus, the initial depth being about 0·10 mm. The responses were largest when the electrode was at a depth of about 0·30 mm, declining significantly with further penetration. The progressive contraction of the x values in input–output plots (Fig. 3*A–C*) obtained with three identical series of constant current pulses, applied at increasing depths (from left to right), show a similar trend in another penetration. These input–output data also reveal a fall in output elicited at greater depths by a given input (cf. the points in Fig. 3*B*, *C*, with those in Fig. 3*A*).

The greater effectiveness of stimulation nearer the surface is consistent with the greater concentration of lower threshold, myelinated axons in the dorsal column than within the nucleus. The second feature, a steeper input–output curve evoked by superficial stimulation may be a reflexion

of the terminal branching of afferent fibres which accounts for the extremely steep initial rise of the input–output curves (cf. Glees & Soler, 1951; Amassian & De Vito, 1957).

Although the input–output data were readily fitted by a smooth power function, they not infrequently showed a significant inflexion at a point between 50 and 75% of maximum input (Fig. 2*B*). This appears to be related to a slower growth of the second component of the orthodromic

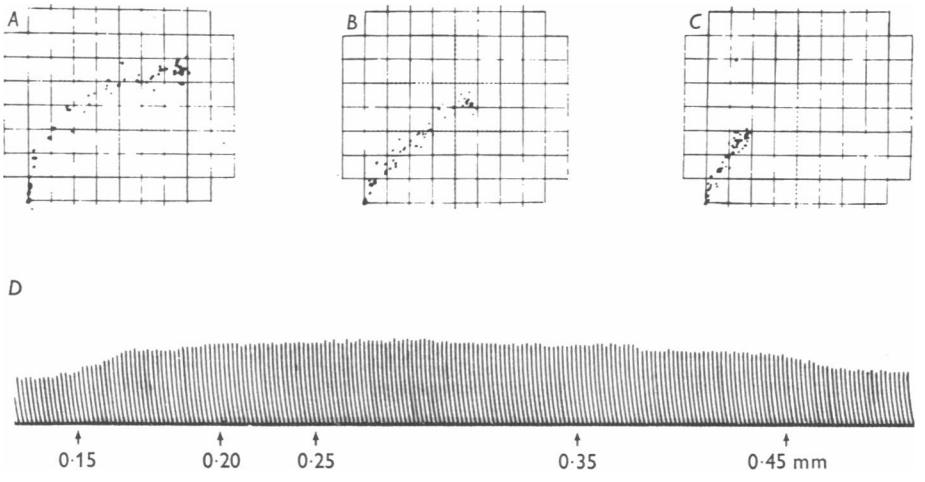

Fig. 3. Responses obtained by moving stimulating micro-electrode to different depths.

A–C: input–output points recorded with identical series of sixteen incrementing constant-current pulses when micro-electrode was inserted into middle third of cuneate at depths of (*a*) 0·1 mm, (*b*) 0·30 mm, (*c*) 0·50 mm.

D: integrated early antidromic responses evoked by 1/sec stimulation (with constant 0·2 msec, 20 μA pulses) at various depths, as indicated. Initially, stimulating micro-electrode was at 0·10 mm; responses at different depths varied between 75 and 90% of maximum that could be evoked at that depth.

response – due mainly, but not entirely, to repetitive firing of many cuneate cells (Amassian & De Vito, 1957; Andersen *et al.* 1964*a*; Galindo, Krnjević & Schwartz, 1968).

Changes in input–output relation under certain abnormal conditions

Poor blood supply. A marked fall in blood pressure ($\ll$ 60 mmHg) is followed by interesting changes in the shape of input–ouput curves. The normal predominantly upward convex shape (with $b < 1$) tends to vanish, being replaced by an upward concave one ($b > 1$).

This is seen particularly clearly when the circulation ceases altogether,

as it did during the series of observations illustrated in Fig. 4, after the deliberate stoppage of the heart by an intravenous injection of $MgCl_2$. (The changes in cuneate transmission were probably not directly caused by Mg^{2+}, since similar observations were made when the blood pressure fell for other reasons.) The input–output data and lines of best fit in Fig. 4*A* and *B* were obtained during the initial control period; the subsequent traces show the corresponding data after the femoral arterial pressure had fallen to zero, as well as for comparison, the initial curve of

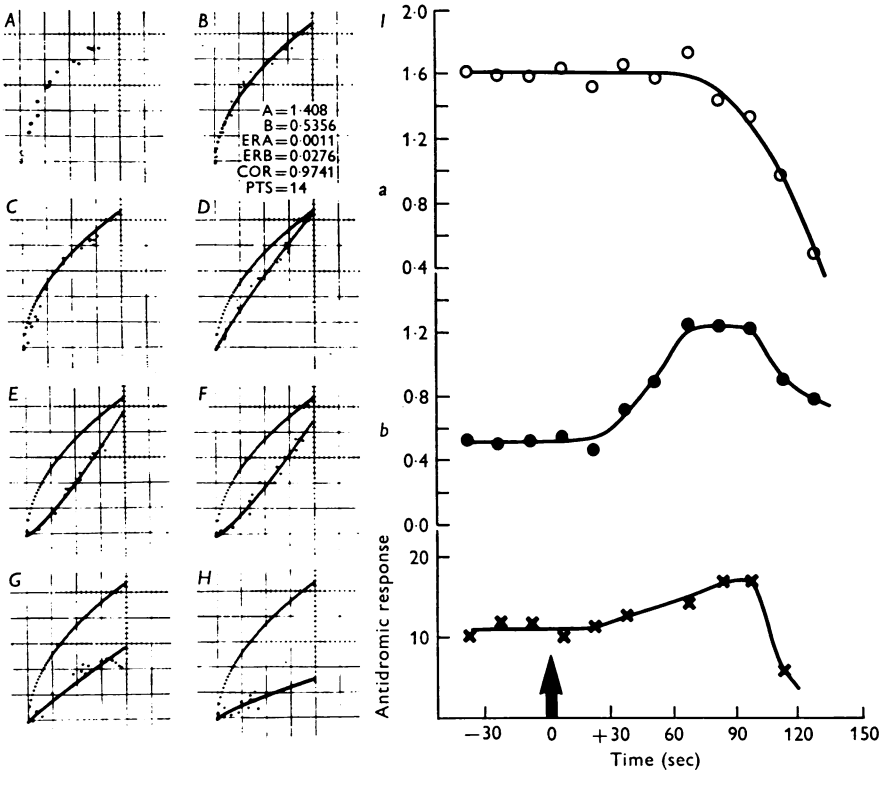

Fig. 4. Changes in shape of input–output relation caused by acute ischaemia.

A, *B*: control data: in *B*, line of best fit is also displayed, together with corresponding values of *a*, *b*, their errors and the correlation coefficient. Same control line is displayed in all subsequent records, as well as experimental points obtained at various times after total collapse of arterial pressure: *C* at 30 sec, *D* 45 sec, *E* 75 sec, *F* 90 sec, *G* 105 sec, and *H* at 120 sec; corresponding lines of best fit are also shown in *D*–*H*. Time course of changes in *a* and *b* coefficients is plotted in graph *I*, as well as size of integrated antidromic response (in arbitrary units) evoked by a constant stimulus (crosses); blood pressure fell to zero at time marked by arrow.

best fit. Within 30 sec (*C*) there was a distinct drop in output, especially for small inputs, the largest outputs being relatively little depressed. This trend led to a flattening (*D*) and then increasing upward concavity of the input–output relation (*E*, *F*).

Thus, for a period of almost 1 min, transmission through the cuneate nucleus had some of the features of pathways where a summation of input is needed to elicit any output (Lloyd, 1943; Lloyd & McIntyre, 1950). Subsequently, the output evoked by large inputs began to collapse (Fig. 4*G*) and transmission practically stopped within 2 min of the onset of total ischaemia, shortly before the complete failure of antidromic conduction (cf. Galindo, 1969; Morris, 1971). The open and filled circles in graph 1 of Fig. 4 show the corresponding values of the coefficients a and b of the curves of best fit. In view of the relative constancy of a, most of the initial changes in transmission are accounted for by variations in b. Close inspection of the input-output points (Fig. 4*E–G*) reveals a progressive shift towards the right, indicating an enhancement of antidromic responses, and presumably a gradual increase in terminal excitability (shown by crosses in Fig. 4*I*). This can be ascribed at least partly to the observed concomitant rise in extracellular K level (cf. also Krnjević & Morris, 1974).

Clearly, the high efficiency of normal transmission through the cuneate depends on active metabolism, which is probably essential for the maintenance of full polarization of afferent terminals (cf. Krnjević & Morris, 1975*a*; Kříž, Syková & Vyklický, 1975). The reduced efficiency of transmission during hypotension or ischaemia is presumably caused by a diminished release of transmitter from depolarized terminals (Eccles, 1964), and perhaps failure of spike generation and invasion of terminals (Krnjević & Miledi, 1959).

Changes in temperature. In four experiments, the temperature of the cuneate region was altered repeatedly by local superfusion with warm or cold physiological saline. Changes in temperature were recorded at the surface of the tissue, and therefore indicate only the maximal possible changes within the nucleus.

The input–output curves consistently became steeper as the surface temperature was raised, and less steep when the temperature was allowed to fall. This is illustrated in Fig. 5*G–I*, where the surface temperature was 40·5° C for *G*, 36° C for *H* and 31° C for *I*. The line of best fit for the data in *H* (36° C) is displayed in the other two traces, to demonstrate more clearly the changes caused respectively by warming and cooling the nucleus.

Substantial associated changes in presynaptic excitability are indicated in these curves by shifts of points along the x-axis: contraction at higher

temperatures and expansion at lower temperatures. A direct illustration of the antidromic responses evoked at different temperatures by a constant stimulus is given by the oscilloscope traces of Fig. 5*A–C*. Unlike the trans-synaptic orthodromic response (lower traces), which remains relatively constant, the antidromic response is clearly reduced at 41° C (Fig. 5A) and sharply enhanced at 31° C (Fig. 5C).

The middle row of traces in the same figure (Fig. 5*D–F*) shows a more comprehensive series of integrated antidromic responses evoked by regularly incrementing current pulses, as well as the surface temperature. In *D*, these antidromic responses diminished when the temperature was

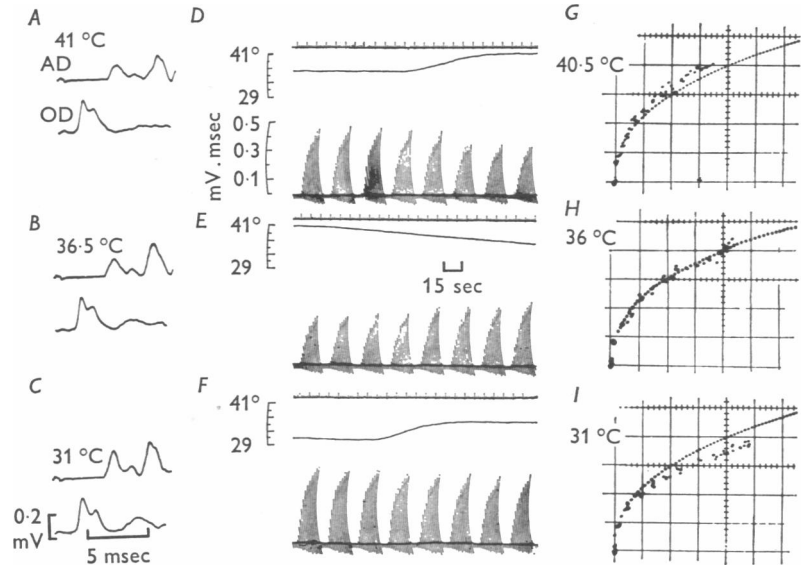

Fig. 5. Effect of temperature changes on antidromic and orthodromic responses and input–output relations of cuneate nucleus.

A–C: upper traces are antidromic responses recorded from superficial radial nerve, lower traces orthodromic responses in medial lemniscus, evoked by 1/sec stimulation through micro-electrode inserted 0·4 mm into cuneate nucleus. Traces were recorded during superfusion of cuneate region with saline at temperatures indicated.

D–F: polygraph traces from same experiment showing (from above down) time scale, surface temperature and integrated antidromic responses evoked by repeated identical series of sixteen incrementing current pulses. Surface of cuneate was superfused with warmer saline in *D*, with cool saline in *E*, and then allowed to return towards normal temperature in *F*.

G–I: computer's display of input–output points obtained in another, similar series, each representing four identical cycles of sixteen incrementing stimuli (total of sixty-four): 'continuous' line is power function giving best fit to control series H.

raised to 41° C. In *E*, they gradually increased as cooler fluid lowered the surface temperature; and in *F*, after reaching their maximum, they returned towards their initial size when the temperature was brought to 37° C.

The full time course of changes in transmission and in terminal excitability in the last sequence of tests is represented by the graph of Fig. 6. Since the best fit values of the exponent *b* varied relatively little (between 0·37 and 0·44), the variations in the curve could be ascribed predominantly to changes in the coefficient *a*. The efficiency of transmission (filled circles) is therefore given by values of *a*, calculated with *b* held constant at its

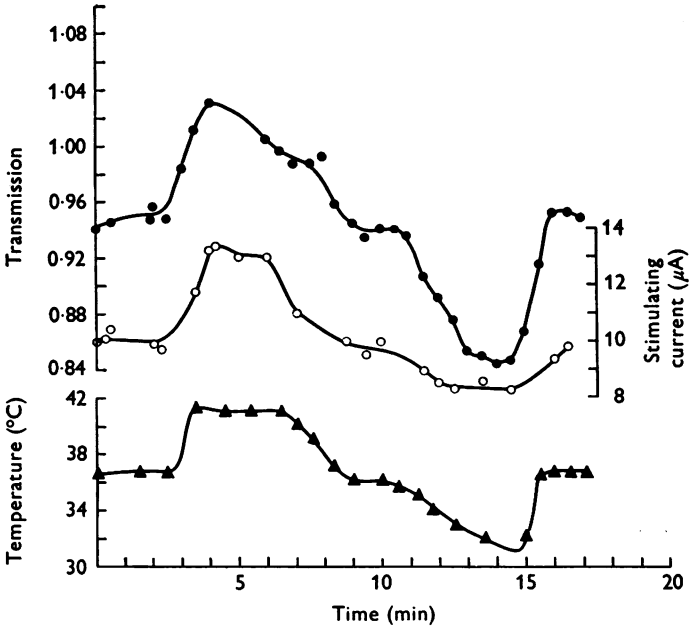

Fig. 6. Graph showing full-time course of changes caused by alterations in surface temperature (series partly illustrated in Fig. 5). Filled circles transmission efficiency represented by coefficient *a* of equations $y = ax^b$ calculated holding *b* constant at initial control value (in this case, 0·400). Open circles: current pulses required to evoke antidromic response of constant amplitude (two thirds maximal during initial control). Triangles: surface temperature.

initial value of 0·40, while the presynaptic changes are defined by the intensity of stimulating current required to evoke a constant antidromic response (open circles). These variables evidently move roughly in parallel with temperature (triangles). Hence, plots of *a* (normalized to 1·0 at 36·5° C) against temperature show a strong positive correlation (Fig. 7*A*,

filled circles); while changes in terminal excitability (calculated from the ratio of currents giving a fixed antidromic response, also normalized to 1·0 at 36·5° C) indicate a very significant *negative* correlation with temperature (Fig. 7*A*, open circles). It is therefore not surprising to find a significant negative correlation between transmission efficiency (*a*) and terminal excitability (Fig. 7*B*).

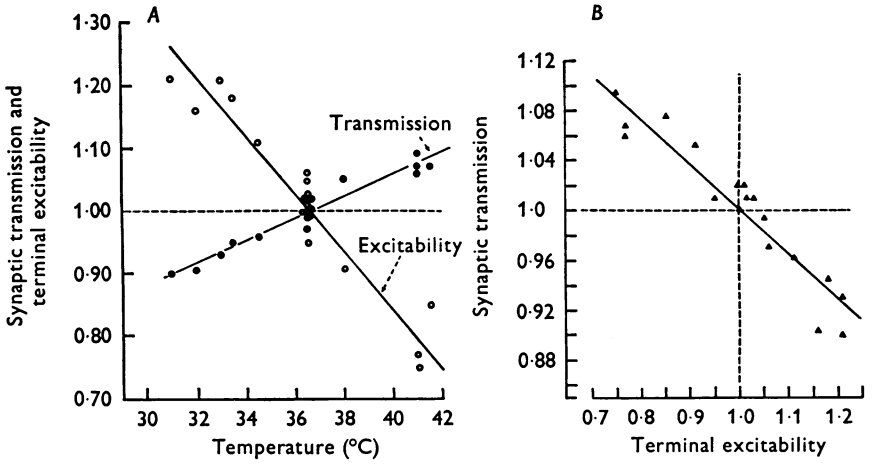

Fig. 7. *A*: graph showing relation between cuneate surface temperature and (open circles) terminal excitability, calculated from reciprocal of currents needed to obtain a constant response, or (filled circles) efficiency of transmission, given by coefficient *a* of best-fitting power function, with *b* held constant at 0·400. Data from last Figure. *B*: graph showing negative correlation between terminal excitability and transmission efficiency, calculated as above; data from same experiment.

TABLE 2. Relation between cuneate surface temperature (*T*), terminal excitability (*E*) (from reciprocals of currents required to evoke a constant submaximal antidromic response) and efficiency of transmission through the nucleus (coefficient *a* in best-fitting power function $y = ax^b$, calculated with exponent *b* held constant at initial control value). Data from three separate series in which surface temperature was varied between 30 and 40° C are regression coefficients, with their standard errors

Series	No. of observations	Depth of cuneate stimulating electrode (mm)	*E* on *T*	*a* on *T*	*a* on *E*
1	19	0·40	−0·0467 (±0·0295)	0·0178 (±0·0017)	−0·370 (±0·030)
2	15	0·14	−0·0388 (±0·0041)	0·0140 (±0·0043)	−0·317 (±0·129)
3	33	0·20	−0·0489 (±0·0019)	0·0138 (±0·0010)	−0·259 (±0·0274)

The slopes of the regression lines from Fig. 7 and their standard errors are given in Table 2 (1st series). The comparable slopes obtained in two other series, while stimulating at different depths in the same experiment, are also listed in Table 2. Qualitatively similar changes were produced by variations in temperature in five other runs, in the same and other experiments. More complex and slower temperature-related changes were

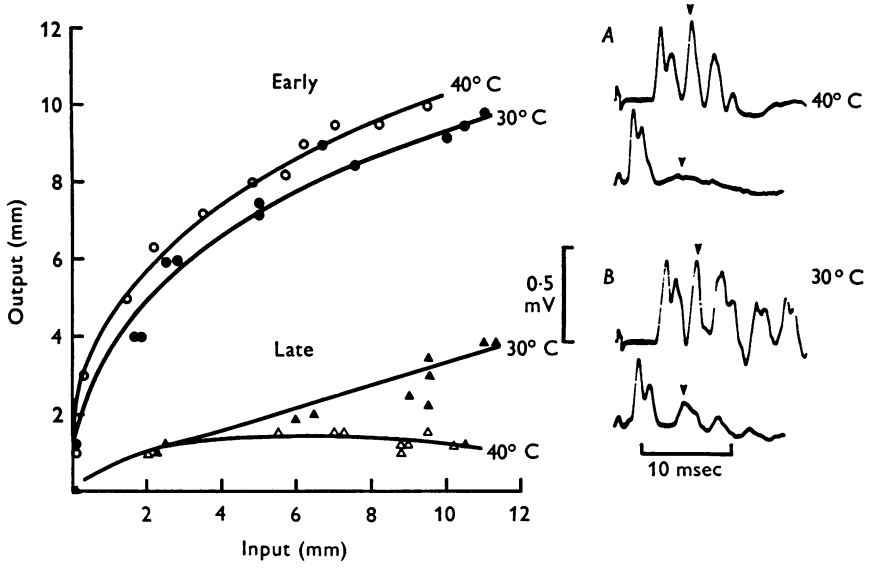

Fig. 8. Graph showing input–output data obtained by measuring peak amplitudes from oscilloscope traces. Open and filled circles, early antidromic and orthodromic responses, at 40 and 30° C respectively. Open and filled triangles, corresponding amplitudes of first peak of antidromic reflex and corresponding late peak in orthodromic record (cf. inset traces *A* and *B* recorded at 40 and 30° C respectively). Arrows mark late peaks measured.

also observed, such as some degree of adaptation when the temperature was held for several minutes at a new level, and subsequently clear indication of hysteresis upon returning to the original level (cf. also Andersen *et al.* 1972*a*).

Warming and cooling led to marked variations in the delayed, antidromic reflex discharge (as is observed with the dorsal root reflex (Brooks, Koizumi & Malcolm, 1955)). This was particularly evident when recording on a slower time base, since the early portion of the reflex may change relatively little (for instance, in Fig. 8, cooling from 40 to 30° C had little effect on the first peak marked by arrows, but it enhanced greatly the later components). A curious related phenomenon is a substantial

improvement in the synaptic efficiency of the reflex discharge. As already pointed out, at a normal temperature the reflex leads to only a small orthodromic response. The graph in Fig. 8 compares the peak orthodromic responses associated with the early direct antidromic discharge (open circles) and those associated with the first antidromic *reflex* (open triangles). The input–output curve resulting from the reflex activity is very different, reaching a maximum of only one tenth of that of the upper curve, and even falling with larger inputs. In contrast to the direct discharge, which as usual

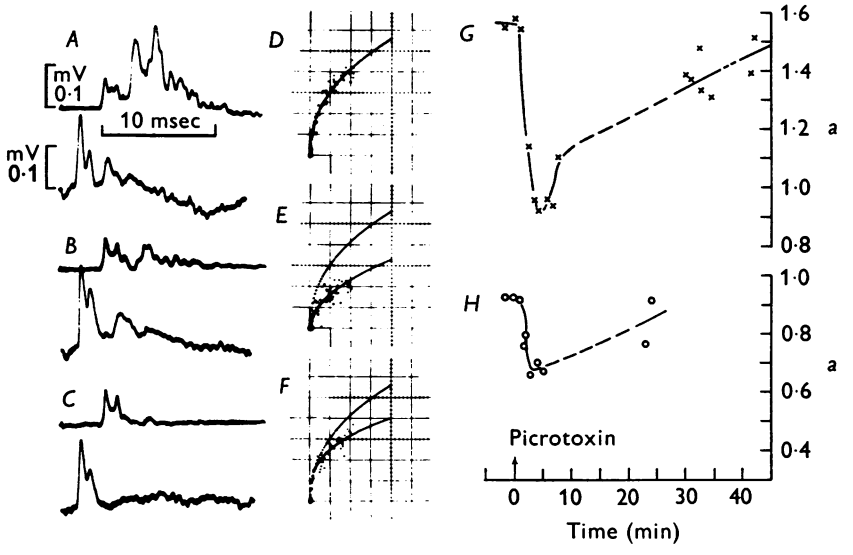

Fig. 9. Effects of picrotoxin on cuneate input–output relations.

A–C: in each record, upper trace is antidromic potential in radial nerve, lower trace orthodromic response in medial lemniscus, evoked by same cuneate stimulus. Note very large antidromic reflex following direct response in *A*. This is much reduced in *B* after first I.V. dose of picrotoxin (1 mg/kg) and almost abolished after a second, similar dose 1 hr later (*C*).

D–F: input–output relations observed in same experiment; *D*, initial control with curve of best fit; *E*, 5 min after first dose of picrotoxin; *F*, 30 min later.

G–H: two examples of time course of changes in input–output relation (*a* calculated for constant *b*) caused by picrotoxin injections (about 1 mg/kg I.V.).

was less effective synaptically at the lower temperature (filled circles) the orthodromic responses associated with the reflex discharge were much augmented by cooling (lower record in *B*, and black triangles in graph), though clearly still small when compared with the first orthodromic response.

Effects of picrotoxin. One possible explanation for the non-linear character of the normal input–output relation is increasingly effective limitation

of output by progressively stronger lateral or recurrent inhibition of cuneate cells (cf. Discussion below). Since it is known that cuneate inhibitory pathways can be blocked by picrotoxin (Banna & Jabbur, 1968; Kelly & Renaud, 1973), it was of interest to see whether this drug would markedly enhance transmission.

The opposite was found: five injections of picrotoxin (0·25–2·5 mg/kg I.V.) in two experiments, consistently reduced the output of the nucleus. The examples of input–output points in Fig. 9*D–F* clearly show this effect, also illustrated by graphs *G–H* in the same Figure.

If the change in output is estimated from values of a calculated with a constant exponent b, the five tests showed a mean reduction of 24·0% (range 12–41%). These depressions of transmission were not accompanied by very marked corresponding changes in terminal excitability: low doses of picrotoxin tended to enhance somewhat the excitability while larger doses had a small depressant effect (cf. Krnjević & Morris, 1975*c*); on the other hand, even in small doses, picrotoxin strikingly inhibited dorsal column relay discharges (Fig. 9*A–C*).

Effects of pentobarbitone. The administration of this general anaesthetic had an unexpected effect. The efficiency of transmission was enhanced rather than depressed. This can be seen from the input–output curves of Fig. 10*B*, recorded before (1) and at various times after an injection of pentobarbitone (2–4) (the curve of best fit for the control points (1) is reproduced in all the traces for reference). After an initial slight depression of transmission, associated with a marked enhancement of antidromic responses (input–output points in (2) move towards the right), and a stabilization of responses, there was a striking and maintained increase in transmission efficiency (3, 4) accompanied by a clear *diminution* in terminal excitability.

The time course of these changes is given graphically in Fig. 9*A* by the values of a (open circles) calculated for a constant exponent, and the stimulating current required to obtain a two thirds maximal antidromic response (filled circles), which is inversely related to terminal excitability. The initial depression of transmission and increase in terminal excitability can be ascribed to the very sharp fall in blood pressure that followed the injection of pentobarbitone (cf. triangles in Fig. 10*A*).

Thus, one again finds some negative correlation between changes in terminal excitability and the efficiency of transmission (Fig. 10*C*). The slope in the left half of this graph is much steeper than the comparable slope of Fig. 7*B* for data obtained at different temperatures; it is also much steeper than in the right half of Fig. 10*C* (initial phase of increased terminal excitability), perhaps because the potentiating action of the anaesthetic was masking the depressant effect of terminal depolarization.

A clear potentiating action of barbiturates on cuneate transmission was observed in six tests out of eight, in six different experiments (once with methohexital, and five times with pentobarbitone). The failure to see such an effect in one case, could be ascribed to an irreversible collapse of the

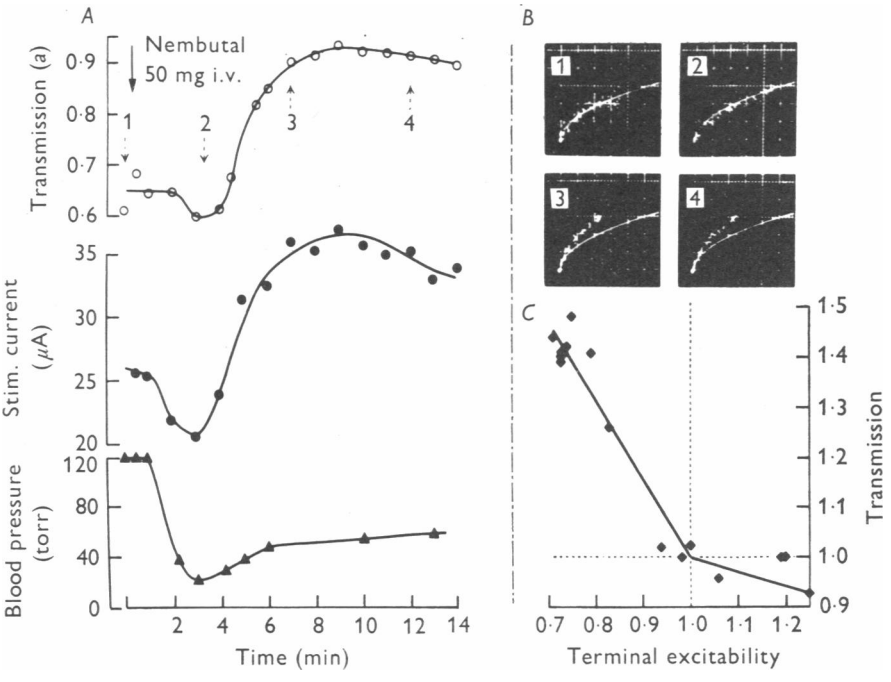

Fig. 10. Effect of injection of intravenous pentobarbitone (Nembutal).

A: open circles, transmission efficiency estimated by *a* coefficient of best-fitting power function, holding *b* at initial control value (0·588). Filled circles: current needed to evoke constant antidromic response (three quarters maximal during initial control) Triangles: blood pressure.

B: examples of input–output points recorded at various times, marked by small arrows with corresponding numbers in graph A. Continuous line is power function of best fit for control values in 1, and is shown for reference in other traces.

C: transmission efficacy as measured by coefficient *a* of power functions (calculated with *b* held constant) plotted against excitability of terminals: latter was estimated from reciprocals of currents needed to give constant antidromic responses (cf. graph *A*). Mean control values are normalized to 1·0.

blood pressure. Changes in terminal excitability were seen less regularly, being conspicuously absent in two experiments in which pentobarbitone was injected after large doses of picrotoxin (these did not prevent the

potentiating action of the anaesthetic). One can conclude that even substantial doses of pentobarbitone tend to improve rather than depress synaptic transmission through the cuneate nucleus.

DISCUSSION

Shape of input–output curves

The very non-linear relation between input and output of the cuneate nucleus confirms the original observations of Amassian & De Vito (1957), but it is evidently not in keeping with Mountcastle's (1966) conclusion that relays in the somatosensory pathway must behave as linear conductors. On the other hand, it is fully consistent with the very high sensitivity of this sensory pathway and its responsiveness over a wide range of stimulus intensities (Mark & Steiner, 1958; McIntyre, 1962). For such a sensory system, a power function with an exponent $\ll 1$ provides a highly appropriate input–output relation (Stevens, 1971).

Similar input–output curves are obtained from other sensory pathways with a high safety factor of transmission and a wide dynamic range: afferent projections to Clarke's column (Lloyd & McIntyre, 1950), the dorsolateral tract (McIntyre & Mark, 1960), and the lateral geniculate (Bishop & McLeod, 1954). They stand in sharp contrast to pathways such as the monosynaptic spinal reflex arc (Lloyd, 1943; Lloyd & McIntyre, 1950; Rall, 1955), where a low safety factor of transmission requires summation of input for a significant output, and the input–output relations are correspondingly sigmoid.

An intriguing feature is that the power functions ($y = ax^b$) which provide a good fit for the input–output relation of the cuneate, on the average have an exponent of 0·5. The square root function has a unique property: its differential coefficient is inversely proportional to the original function. Therefore if one defines the sensitivity of the system at any given level of stimulation by dy/dx, this must be inversely proportional to the output at that level. In other words, the system operates as if its gain were automatically set by an output volume control.

The mechanism of operation is by no means fully clear. A simple inhibitory feedback activated by the cuneate output would have the appropriate limiting action. But strong recurrent inhibition is not a feature of cuneate cells (Amassian & De Vito, 1957; Gordon & Paine, 1960; Andersen *et al.* 1964*a*). Moreover, only the later slower components of the cuneate response could be much affected by any conceivable inhibitory action, whether of the feed-back, or more likely, feed-forward type. Our observation that picrotoxin tended to depress rather than enhance transmission is further evidence that the normal non-linear relation is probably *not* determined by inhibitory mechanisms.

A different kind of mechanism leads one to expect a non-linear input–output relation. The remarkable sensitivity of cuneate cells to the excitation of very few

peripheral fibres (Amassian & De Vito, 1957; McIntyre, 1965) indicates a very high probability of transmission, as well as a wide divergence of input through numerous terminal branches of single afferent fibres (cf. Glees *et al.* 1951). Since there is only a limited number of cuneate cells, many terminals must connect with a given neurone. This combination of high degrees of both divergence and convergence inevitably leads to progressive occlusion with increasing input. Assuming a 100% probability of transmission, a simple random connexion of x input fibres to n cells would give a relation of the following general type (cf. Feller, 1950, p. 34):

$$y = n\left[1-\left(1-\frac{1}{n}\right)^{x}\right]$$

(where y is the number of output cells excited by a given number of input fibres). However, although this function gives a markedly non-linear input–output curve, it is also non-linear on log.–log. plots:

$$\frac{\mathrm{d}\log y}{\mathrm{d}\log x} = -\frac{x(1-1/n)^{x}\log(1-1/n)}{1-(1-1/n)^{x}}.$$

The observed square-root relationship must therefore be the result of a more complex organization of afferent connexions in the nucleus. It is relevant in this context that very similar power functions also describe well the input–output relations of several cutaneous receptors (Werner & Mountcastle, 1965; Harrington & Merzenich, 1970), where an inhibitory control is hardly likely to be present.

Although the technique used in our experiments had the signal advantage of measuring simultaneously both terminal excitability and input–output relations, the sampling of input was probably not always representative of the total effective input. However, in similar experiments, where a better approximation of input was obtained by stimulating (and recording from) a peripheral nerve, input–output relations proved to be quite comparable (M. E. Morris and R. Werman, unpublished observations).

Temperature effects

Working over a somewhat smaller range of temperatures than Andersen *et al.* (1972*a*, *b*), we have confirmed their observation that cooling lowers the efficiency of transmission through the cuneate nucleus. In addition, it was shown that raising the temperature above the normal level improves transmission. In fact, the efficiency of transmission appeared to be a relatively simple function of temperature (Fig. 7*A*). Since these tests were performed on decerebrate cats, the observations must reflect true changes in intrinsic efficiency of transmission, and not some secondary effect, such as temperature dependent variations in anaesthetic action.

The only major difference between our observations and those of Andersen *et al.* (1972*a*, *b*) concerns the presynaptic events. In contrast to their finding that cooling *diminishes* terminal excitability, we have consistently seen an increase in antidromic responses during cooling, and a decrease during warming.

A possible explanation for the discrepancy between our findings and those of Andersen *et al.* (1972*a*, *b*) is that the temperature dependence of terminal excitability may be changed by anaesthesia. Alternatively, temperature-related variations in electrode resistance in their experiments may have altered the effectiveness of the stimulating pulses. Such changes were minimized in the present experiments by the use of constant-current pulses.

The clear negative correlation between terminal excitability and the efficiency of transmission observed under these conditions agrees with many previous observations at other sites (Liley, 1956; Hagiwara & Tasaki, 1958; Eccles, 1964; Hubbard, 1970). However, the behaviour of the cuneate relay is not typical of all central synapses. The opposite has been observed in at least two instances: cooling enhances transmission in the spinal monosynaptic pathway (Brooks *et al.* 1955; Pierau, Klee & Klussmann, 1969) and in the granule cell pathway of the cerebellar cortex (Eccles, Rosén, Scheid & Taborikova, 1975). Such differences in behaviour may be caused by different contributions of electrogenic Na–K pumping to the polarization of various nerve terminals. Studies on some molluscan neurones have shown that whereas cooling causes depolarization when the electrogenic pump is operating, the same cells are hyperpolarized by cooling after inactivation of the pump (Carpenter, 1970; Gorman & Marmor, 1970).

Anaesthesia

The striking potentiation of transmission by pentobarbitone (and methohexital) is of great interest. Although surprising, it is not altogether out of keeping with some previous observations. Thus, a similar relative change between input and output of the cuneate is evident in some of the data published by Galindo (1969) (cf. his Fig. 5). More recent experiments on the neuromuscular transmission in the frog (Thomson & Turkanis, 1973) have shown an enhancement of transmission by phenobarbitone, which was also ascribed to an enhancement of transmitter release.

The commonly associated marked depression of terminal excitability by pentobarbitone (see also Galindo, 1969) provides another possible example of potentiation of transmission correlated with presynaptic hyperpolarization. The mechanism of the presumed hyperpolarization could be any one of the following: a rise in intracellular free Ca, leading to an increase in K^+ conductance (cf. Krnjević, 1974), a direct effect of pentobarbitone on the terminal membrane (Barker & Levitan, 1975), or an activation of electrogenic Na–K pumping. Whatever its precise nature, this mechanism is much more prominent in the primary afferents in the cuneate than in terminals on spinal motoneurones, where comparable changes in excitability have not been consistently detectable (cf. Somjen, 1967; Løyning, Oshima & Yokota, 1964) and pentobarbitone appears to

depress transmitter release (Weakly, 1969). According to a very recent study, pentobarbitone has a depolarizing action on afferent terminals in the frog's spinal cord (Nicoll, 1975).

The difference between observations on these various pathways can of course be correlated with their markedly different sensitivity to general anaesthetics. Unlike the spinal monosynaptic reflex arc, the sensory pathway to the cortex via the dorsal column, cuneate and thalamus is very resistant to general anaesthetics (Mark & Steiner, 1958; Randt & Collins, 1959; Angel & Unwin, 1970). In general, primary cortical responses evoked by afferent activity tend to be enhanced by anaesthesia (Brazier, 1954; Domino, 1967). Such facilitation of transmission could be due at least in part to the potentiating action of pentobarbitone described here.

On the other hand, an excessive reduction in terminal excitability may cause some failures of terminal invasion and thus block further transmission (cf. the action of CO_2, Morris, 1971). Different combinations of presynaptic potentiation and depression, as well as of post-synaptic depression (cf. Galindo, 1969), help to explain the protean manifestations of pentobarbitone anaesthesia at various sites in the central nervous system.

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