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FACILITATION OF CORTICAL RESPONSES BY COMPETING STIMULI

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During investigations of transmission in the sensory pathway of the rat, it was found that when an electrical test stimulus was applied to a forefoot the response to it, recorded from the dorsal surface of the medulla near the cuneate nucleus, could be reduced in size by stimulation of the cerebral cortex on the opposite side (Dawson, 1958). This effect occurred even when the animal was deeply anaesthetized. Similar results have been described in unanaesthetized, curarized, cats by Scherrer & Hernández-Peón (1955). Modifications of transmission in the spinothalamic pathways have been investigated by Hagbarth & Kerr (1954) and the alteration of responses of single units in the cuneate nucleus have been examined by Towe & Jabbur (1961) and Jabbur & Towe (1961).

An electrical stimulus to the cerebral cortex, such as that used to modify the response of the cuneate nucleus to a test stimulus (Dawson, 1958) is unlikely to produce a natural pattern of discharge in the cerebral cortex itself, or in the pathways leaving it. Investigations were therefore begun to see whether similar alterations of the responses in the cuneate nucleus could be produced by stimulating the body surface instead of the cerebral cortex. This also allowed records to be made of the cortical responses to the test stimuli, to see how far their size was related to the size of the responses in the cuneate nucleus. The evidence to be presented shows that, under the conditions of these experiments, stimuli applied to various parts of the body surface have little or no effect on the responses of the cuneate nucleus to test stimuli applied subsequently to a forefoot. On the other hand, as has been reported elsewhere in abstract (Dawson, Podachin & Schatz, 1959), the responses of the cerebral cortex to the test stimuli were

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found to be modified, and in some respects greatly increased, by preceding stimulation of the body surface.

METHODS

The experiments have been carried out entirely on albino rats approximately 200 g in weight. Young animals have been used because the state of development of the atlas and axis, and of the base of the skull, allows easier access to the medulla than in older animals. Anaesthesia was induced with trichloroethylene vapour in air and maintained, after a tracheal cannula had been introduced, by blowing a steady stream of the anaesthetic across the end of a T-piece connected to the cannula. The depth and rate of breathing were not controlled by the anaesthetic apparatus. The animal's temperature was maintained by an electric heater controlled from a rectal thermometer. The cerebral cortex of one side was exposed and access to the medulla was obtained by removal of the atlanto-occipital membrane and the arch of the atlas. The cerebral cortex and the medulla were covered by a common pool of liquid paraffin. Sufficient access to the cuneate nucleus, without removing any of the occipital bone or of the posterior lobe of the cerebellum, was usually obtained by tilting the animal's head, nose downwards. The head was held by means of a plug in each external auditory meatus and a bar passing under the hard palate immediately behind the incisor teeth; the palate bar and ear plugs lay in a plane 20° from the horizontal. The head holder and the platform on which the animal rested were mounted on two screw-operated slides which gave movements in the horizontal plane, one parallel to the long axis of the animal and the other perpendicular to it. The scales on the slides were graduated in 1 mm intervals with 0·1 mm verniers, and they were arranged to read zero in both axes when the centre point of the distance between the ear plugs fell on the vertical axis in which the micro-electrode moved. Vertical movement of the micro-electrode was carried out first by a slide with a coarse screw, and when this was set and locked, by a slide with a fine screw calibrated in steps of 5 μ. The micro-electrode for recording from the medulla was a glass pipette with an outside diameter at the tip of 2–5 μ, filled with 12 % NaCl solution and having a resistance between 1 and 4 MΩ. It was connected through a cathode follower to a resistance–capacity-coupled amplifier. The high-frequency response of the amplifier was such that the deflexion produced by a rectangular voltage pulse at the input reached 90 % of its full amplitude in 0·1 msec. The low-frequency response was usually set so that the deflexion due to a rectangular input fell to 90 % of its full amplitude in 5 msec, equivalent to a time constant of 0·032 sec. Records from the cerebral cortex were made through fine silver wires, fused at their tips into small balls, and connected to a similar RC amplifier.

The body surface was stimulated either mechanically, by stroking, rubbing or pinching the skin, or electrically. The electrical stimuli were rectangular voltage pulses of 0·05 or 0·1 msec duration, applied through an isolating transformer to small strips of lint soaked in a saturated solution of salt and wrapped round fore- or hind-foot digits. The cerebral cortex was stimulated electrically by rectangular voltage pulses of 1 msec duration applied through an isolating transformer to the silver wire electrodes used at other times for recording the cortical potentials. The voltage pulse actually reaching the cortical electrodes was not rectangular towards its end, as the isolating transformer had insufficient primary inductance at the voltages used to maintain the shape of any pulse lasting longer than 0·5 msec. The grouping and timing of the various stimuli was controlled by digital timing devices (Pitman, 1958). In the photographs from the final cathode-ray tube display a number of responses were usually superimposed to show the degree of variation which occurred at lighter levels of anaesthesia.

RESULTS

Responses in the cuneate nucleus

When an electrode was placed on the surface of the dorsal aspect of the medulla, at a point 0·5–0·75 mm lateral to the mid line and between the level of the obex and 1 mm caudal to it, electrical stimulation of a forefoot gave rise to potentials at the electrode of the type shown in Fig. 1*A*. In this record 10 traces were superimposed; each shows a response to a single electrical stimulus to two digits of the right forefoot. The interval between successive stimuli was 1 sec and the point in the traces at which the stimuli were applied is shown by the downward spike in the time scale; this corresponds with the start of the stimulus escape in the records. A small upward deflexion occurs in the record 1·5 msec after the start of the stimulus escape. This indicates that the active electrode in the medulla became positive with respect to other parts (in this and in all succeeding records relative positivity of the active electrode is indicated by an upward deflexion). This positive potential lasted between 0·5 and 1 msec and it was succeeded by a much larger negative potential at the active electrode. This negative potential reached its first peak 2–2·5 msec after the stimulus, then a series of smaller deflexions lasting 0·5–1 msec occurred before the potential returned to zero. The first, positive-going, potential was relatively resistant to asphyxia and would persist for 5 min or more if the trachea was clamped. In contrast, the second, negative-going potential disappeared within 1·5 or 2 min in the same conditions. It seemed likely therefore that the initial positive wave represented the arrival at the nucleus of the first part of the volley travelling in the posterior columns, and that the negative wave represented early post-synaptic events in the nucleus. Movement of the stimulus from the ipsilateral forefoot to the contralateral forefoot, or to either hind foot, caused all phases of the potential to disappear. The characters of these responses appear to be closely similar to those described by Therman (1941) and Amassian & De Vito (1957).

Effects of cortical stimulation. At a depth of anaesthesia that prevented the animal withdrawing a hind foot which was pinched firmly, electrical stimulation applied to a forefoot gave rise to a relatively localized potential change in the contralateral cerebral cortex. An electrode placed to pick up this response with maximum size and minimum latency recorded no potentials from stimuli applied to the hind foot on the same side, or to any other part of the body surface. It was therefore probably over the primary somatic receiving cortex for the forefoot. When a 1 msec electrical stimulus was applied to an electrode placed in this way, so as to make it negative with respect to an electrode rostral or medial to it, it was found that test

stimuli applied to the forefoot during the next 5 or 10 msec gave reduced responses in the cuneate nucleus. This effect was increased if, instead of a single stimulus, a train of stimuli was applied to the cortex before the test stimulus. In the records in Fig. 1*B* and *C* five stimuli at 10 msec intervals were applied to the cerebral cortex. The last stimulus in each train occurred just under 5 msec before the test stimulus was applied to the forefoot (Fig. 1*B*). At this separation the initial positive wave in the response in the cuneate nucleus was not reduced in size but the negative

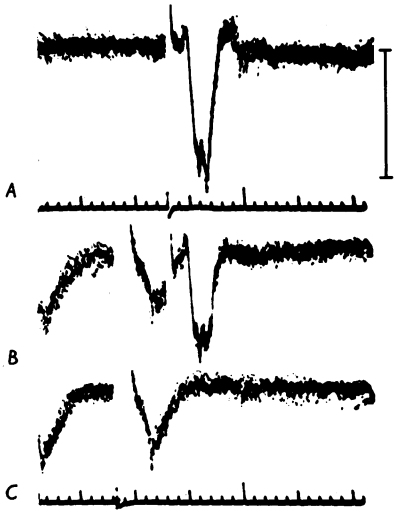

Fig. 1

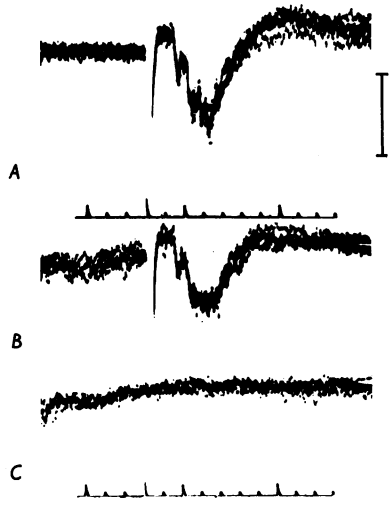

Fig. 2

Fig. 1. The records were made through a glass micropipette from the surface of the medulla over the right cuneate nucleus. In each trace are superimposed 10 responses. In *A* single electrical test stimuli were applied once per second to the right forefoot. In *B*, 5 stimuli at intervals of 10 msec were applied to the left sensory cortex before each test stimulus was applied to the forefoot. The responses to the test stimuli are reduced in size. In *C* are shown the potentials produced in the medulla by the last two cortical stimuli; no forefoot stimuli were applied. The time scales show intervals of 1 and 5 msec and the vertical bar shows the deflexion produced by an input of 1 mV. In this and in all subsequent records a relative positivity of the micro-electrode is recorded as an upward deflexion.

Fig. 2. The records were made under the same conditions as those in Fig. 1, but in a different animal. Five responses are superimposed in each sweep. In *A* the test stimuli alone were applied to the forefoot. In *B* the test stimuli were preceded by 10 stimuli at 5 msec intervals applied to the sensory cortex. The last of the cortical stimuli occurred 8 msec before the test stimuli; the reduction is less than in the experiment of Fig. 1 and is confined to the later parts of the test responses. In *C* the cortical stimuli were applied alone, the last of the train fell 5 msec before the start of the time scale, which shows 1 and 5 msec intervals. The vertical bar shows the deflexion due to an input of 500 μV.

deflexion following it was reduced by 25–30 %. The reduction appears to be greatest in the second and third peaks of the negative deflexion.

From the records in Fig. 1*C*, in which the cortical stimuli alone were applied, it can be seen that they produce a considerable negative potential in the electrode applied to the medulla. The structures responsible for these potential changes produced by the cortical stimuli were not clear from the present experiments, but from the sequence of events when the micro-electrode was pushed into the medulla, it seemed that they lay deep to the cuneate nucleus. The last of these negative potentials produced by the cortical stimuli had subsided by the time at which the response to the forefoot stimulus occurred. It therefore seems likely that the modification of the response to the forefoot stimulus by a preceding train of cortical stimuli was not due to a simple summation in the record of the potentials produced by the cortical and peripheral stimuli. This is seen more clearly in the records in Fig. 2, from a different animal, in which the same strength of stimulus was applied to the forefoot (Fig. 2*A*) but the last cortical stimulus occurred 8 msec before the stimulus to the forefoot. Figure 2*C* shows that the last potential due to a cortical stimulus occurred before the start of the record and therefore the reduction of the response to the forefoot stimulus which occurred when both cortical and peripheral stimuli were applied (Fig. 2*B*) is recorded on a flat base line. The records also show that when 8 msec separated the last cortical stimulus from the forefoot stimulus the reduction of the first negative potential of the response was less than when the interval was 5 msec. The modification of the cuneate responses lay largely in a reduction of the later peaks of the negative wave.

When the interval between the last cortical stimulus and the forefoot stimulus was 10 msec or more, the cortical stimulus was not seen to affect the cuneate mass response. However, an absence of change in a mass response from many units may mean no more than that there was a balance between the number of units excited by the cortical stimulus and the number inhibited. Certainly when the activity of small numbers of units was observed some of them were seen to be inhibited for 40 msec or more after a stimulus to the primary somatic receiving area of the cerebral cortex. The records shown in Fig. 3 were made from units in the cuneate nucleus which could be fired by light pressure on the rostral aspect of the upper part of the right forelimb. During the time these records were made the units were firing continuously with a respiratory rhythm, apparently due to mechanical stimulation by the respiratory movements of the animal. When 10 sweeps were superimposed (Fig. 3*A*) the spikes were more or less evenly distributed throughout the record. A single electrical stimulus to the somatic receiving area for the right forelimb (Fig. 3*B*) produced a silent period of 40 msec in the superimposed

record. The same units were inhibited for rather longer when a single peripheral electrical stimulus was applied to the digits of the forelimb, well away from the place where the pressure would excite them (Fig. 3*C*).

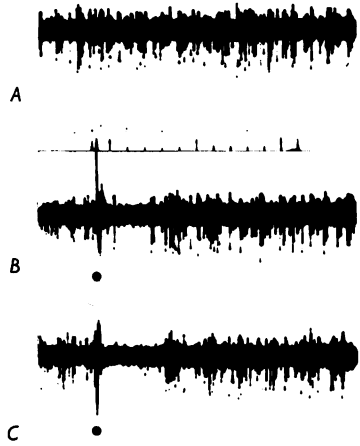

Fig. 3. The records were made through a micro-electrode with a tip diameter of 2μ, inserted 0·35 mm below the surface of the medulla. The units recorded could be fired by mechanical stimulation of a small area of the skin of the forelimb; in the records they were firing with a rhythm produced by the respiratory movements of the animal. Ten sweeps are superimposed in each record. *A* shows the scatter of the discharges throughout the traces. In *B* single electrical stimuli were applied to the opposite sensory cortex, on each sweep, at the point marked by the dot. A pause in the discharge of the units followed all the cortical stimuli. In *C* a single electrical stimulus was applied to the forefoot, remote from the region from which the units could be excited by mechanical stimulation. The units pause longer after the peripheral than after the cortical stimulus. The time scale below *A* shows time intervals of 20 msec.

Responses in the cerebral cortex

At the depth of anaesthesia used, the potentials evoked from the primary somatic receiving cortex by an electrical stimulus to a forefoot varied considerably. In Fig. 4 three sets of records are shown; in each record 10 responses were superimposed. Records *A*, *B* and *C* are sets of responses to single electrical stimuli applied to the right forefoot. The stimulus strength used was insufficient to produce any withdrawal in a lightly anaesthetized animal and the responses disappeared if the posterior part of the spinal cord was cut through on the same side as the forefoot stimulated. The majority of the responses showed a sharply rising positive potential, which began 4–5 msec after the stimulus and reached its peak at 6–7 msec. After this first peak the potential fell and then a second positive wave occurred with its peak at 15 msec after the stimulus. The fall between the two positive peaks sometimes reached the base line, but

frequently did not. In records *D*, *E* and *F* the test stimulus to the forefoot was preceded and accompanied by stimulation of some other part of the body surface. In record *D* the preceding stimulus was a pinch applied to the left side of the face. In record *E* a pinch was applied to the right hind foot and in record *F* to the left hind foot. In all three cases the initial positive potential was cut short by a rapidly developing negative potential going well below the base line. The size of this alteration in the cortical responses was apparently independent of the part of the body which was

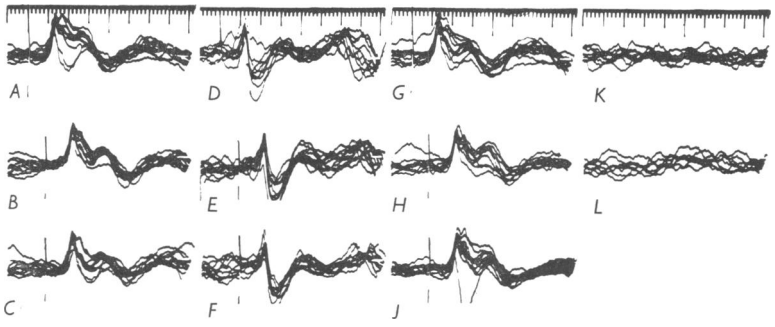

Fig. 4. The potentials were recorded from an active electrode (+, up) over the left primary somatic sensory cortex. In records *A*–*J* 10 responses to a single electrical stimulus applied to the right forefoot have been superimposed. In records *A*, *B* and *C* the forefoot stimuli alone were applied. During record *D* the left side of the face was being pinched. In *E* the right hind foot, and in *F* the left hind foot was being pinched. The negative-going second phases of the responses were increased, regardless of the site of the pinches. Records *G*, *H* and *J*, taken soon after *D*, *E* and *F*, without pinching, show a return of the responses to the initial form in *A*, *B* and *C*. Records *K* and *L*, taken without the right forefoot electrical stimulus but during pinching the left face and left hind foot, show no systematic cortical potentials. The time scales show intervals of 1, 5 and 20 msec.

pinched. That the pinches alone did not produce any recognizable potentials in the primary receiving area was shown by records *K* and *L*. Control records *G*, *H* and *J*, taken shortly after *D*, *E* and *F*, showed that the cortical responses to the forefoot stimuli alone had returned to the form they had before the pinches were applied. In one of the 10 control responses in record *J* the initial positive wave was followed by a large negative wave without any stimulus having been applied before the forefoot stimulus. That such a spontaneous change was rare may be seen from the fact that it occurred only once in the 60 responses shown in records *A*, *B*, *C*, *G*, *H* and *J*. On the other hand, the change produced by antecedent stimulation occurred in 7 of the 10 responses in record *D* and in all 20 responses in records *E* and *F*.

The same modification of the cortical potentials could be produced by other stimuli than pinching, such as firm rubbing, or electrical stimuli, provided that they were strong enough. The effect of preceding electrical stimulation on the cortical responses to forefoot stimuli is shown in Fig. 5. The upper record in each pair shows the responses of the cuneate nucleus and the lower record the cortical responses. In *A* the forefoot stimuli alone were applied and 3 of the 10 superimposed cortical responses showed

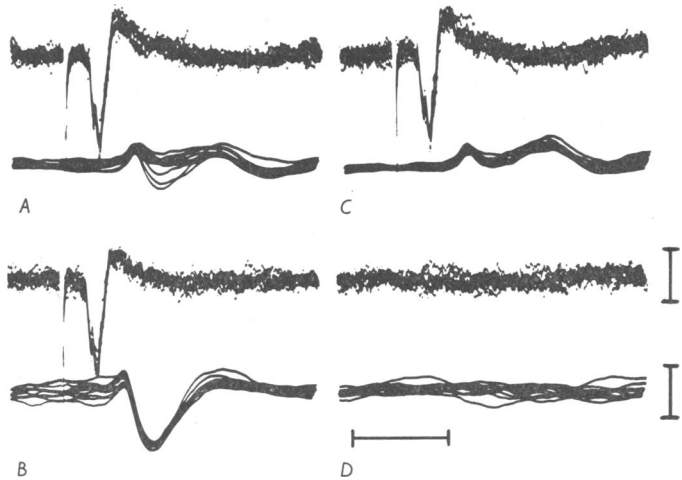

Fig. 5. The upper record of each pair shows the responses recorded through a microelectrode from the surface of the medulla over the right cuneate nucleus. The lower record shows the responses from an active electrode over the left primary sensory cortex. In *A*, *B* and *C* electrical stimuli were applied to the right forefoot. In *B* and *D* trains of 30 stimuli at 3 msec intervals were applied to the right hind foot, ending 45 msec before the test stimuli. The hind-foot stimuli alone produced no systematic cortical potentials at the time of the test response (*D*) but the test responses were increased when they followed the hind-foot stimuli (*B*). After the hind-foot stimulus was stopped the test responses returned to their original size but showed less variability (*C*). No comparable change in size occurred in the cuneate responses when the cortical responses were facilitated. Ten sweeps superimposed in each record. The upper vertical bar in *D* shows a calibration of 200 mV for the medullary responses, the lower, 400 mV for the cortical responses. The horizontal bar under *D* shows a time of 10 msec.

negative-going second phases which reached, or passed, the base line. In *B* the test stimuli were preceded by a train of 30 electrical stimuli, 3 msec apart and applied to the right hind foot. The last stimulus of the train to the hind foot occurred 45 msec before the test stimulus to the forefoot. After this stimulation of the hind foot, all the cortical responses showed large negative second phases and their peak latency was reduced from 7·2 to 6·1 msec. The control records in *C* show that after the hind-foot stimulus was stopped none of the cortical responses to the forefoot stimuli

had negative second phases below the base line. In *D* the records were made after the hind-foot stimuli alone had been applied, and they showed no systematic potentials, either in the cortex or the nucleus.

The records in Fig. 5 show that the increase in the cortical response produced by the hind-foot stimuli was not associated with any comparable change in the size of the cuneate response. Indeed, when the antecedent stimuli were applied to the same site as the test stimuli the cortical responses were still increased, though the responses in the cuneate nucleus were reduced. This is shown in the records in Fig. 6. In *A* the test stimulus

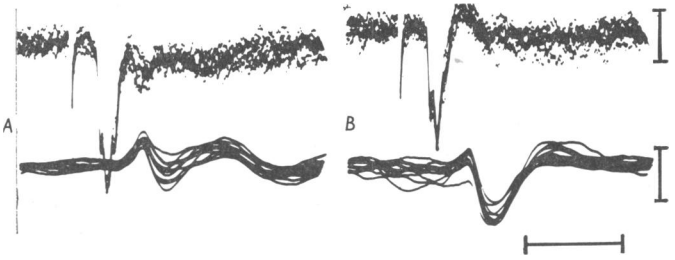

Fig. 6. Records from the same preparation as those in Fig. 5 and under the same conditions, except that the train of conditioning stimuli was applied to the same electrodes as the test stimuli on the forefoot. In *A* the test stimuli alone were applied. In *B* the test stimuli were preceded by 30 conditioning stimuli at 3 msec intervals, the last 45 msec before the test stimulus. In *B* the cortical test responses are increased in size, in spite of a reduction in size of the cuneate test responses. 10 sweeps superimposed. The upper calibration in *B* is for 200 μV, the lower for 400 μV and the horizontal bar represents 10 msec.

alone was applied to the right forefoot, while in *B* a series of 30 stimuli at 3 msec intervals was applied to the same electrodes, finishing 45 msec before the test stimulus. In record *B* the initial negative wave of the cuneate response was 15% smaller than that in *A*, but the negative second phase of the cortical response was regularly increased in size. Therefore, in so far as transmission through the cuneate nucleus may be related to the size of the mass responses in it, it seems that the changes in form and size of the cortical responses were not due to any great increase in the volley leaving the nucleus. The changes in the cortical responses could, however, have been due either to an increased volley reaching the cortex, as a consequence of altered transmission in the thalamus, or to a change in the state of the cortex itself. That either or both of these may occur is shown by the following experiments.

Effect of stimulus strength on cortical responses. A series of records taken over a short period with a constant level of anaesthesia, but with increasing stimulus strength, is shown in Fig. 7. In Fig. 7*A* the stimulus strength was just below threshold for the production of a response in

either the cuneate nucleus or the cortex. In *B*, with a stimulus just above threshold, the cortical response consisted of two positive waves with a small and variable dip between them. Further increase of stimulus strength, up to a value giving maximum value in *F*, caused a progressive increase in the relative size of the negative second wave and a decrease in the variability of the responses. A change of strength of the test stimulus alone, from just above the threshold to maximum, may therefore produce the same alterations in the cortical responses as are produced by antecedent stimulation of other parts of the body surface.

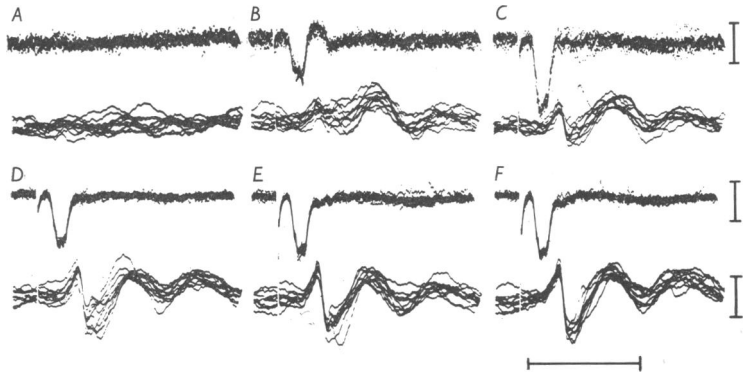

Fig. 7. The records show responses to electrical stimuli applied to the right forefoot. The responses were recorded from the right cuneate nucleus, upper trace, and the left cerebral sensory cortex, lower trace. The anaesthetic was unchanged throughout, but the stimulus strength was increased from near threshold (8 units) in *A* to over twelve times threshold strength (100 units) in *F*. As the ascending volley increased in size the negative-going second wave of the cortical response increased in size proportionately more rapidly than did the positive-going initial wave. The calibration in *C* shows 200 μV for the medullary responses in records *A*, *B* and *C*. The upper calibration in *F* shows 400 μV for the medullary responses in *D*, *E* and *F*. The lower calibration in *F* shows 200 μV for all the cortical records *A* to *F*. The horizontal line shows 20 msec.

Effect of depth of anaesthesia. When the stimulus was kept constant and the depth of anaesthesia was altered the cortical responses changed in the same way as with altered stimulus strength. In the records in Fig. 8, which were made from the same preparation as those in Fig. 7, the stimulus strength was kept constant at the value used in Fig. 7*F*. When record *A*, Fig. 8, was made the anaesthetic level had been deep for some time. In these conditions the cortical responses showed a prolonged positive wave with very little negative-going dip after the first rise. Record *A* was taken 1 min after the concentration of trichloroethylene had been reduced, and records *B*–*E* were made over the next 20 min. In record *B*, 90 sec after the concentration of anaesthetic was reduced, all the 10 superimposed

records showed a clear trough, reaching approximately to the base line and separating two positive peaks. In record *C*, 4 min after the reduction of anaesthetic, the response became variable; 8 of the 10 showed large negative-going second phases and in 2 the negative wave was small or absent. This variability continued over the next 10 min, but at 20 min (Fig. 8*E*) the variation is less and all 10 responses showed negative second phases going below the base line. After this record the anaesthetic was turned off and at 4 min, when signs of spinal reflex excitability were returning and the animal would just withdraw a foot which was pinched firmly, the records in Fig. 8*F* were made. They show stereotyped responses,

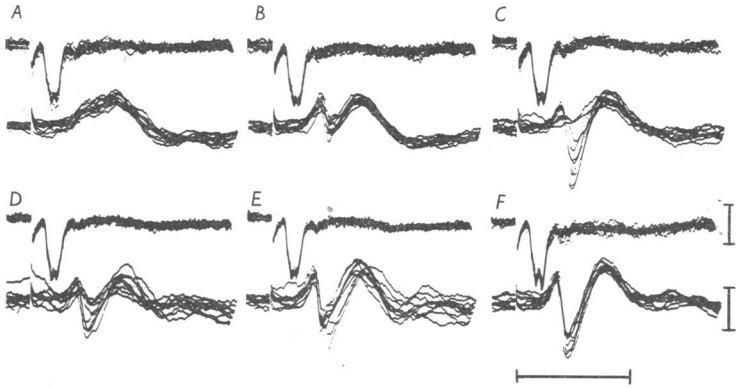

Fig. 8. The records show a series of sets of cuneate (above) and cortical (below) responses to stimuli of fixed strength, twelve times threshold as in Fig. 7*E*, and from the same preparation. After a period of deep anaesthesia the concentration of anaesthetic was reduced, and records *A*–*E* were taken 60 sec, 90 sec, 4 min, 10 min and 20 min after this reduction. The anaesthetic was then turned off, and 4 min later, when the first signs of withdrawal to a pinch appeared, record *F* was made. The upper calibration in *F* shows 400 μV for the medullary record, the lower, 200 μV for the cortical records. The time calibration shows 20 msec.

all of which have relatively large negative second phases with little variation in amplitude. Together with this increase in the size of the negative-going second phase there is a decrease in latency both of the start of the responses and of the first positive peak. The latency of the start diminished from 6·1 msec in *A* to 4·1 msec in *F*, and the latency of the first positive peak from 10·2 msec in *A* to 6·8 msec in *F*.

The same set of records showed that a change of the depth of anaesthesia of this degree also affected the responses of the cuneate nucleus to the test stimuli applied to the forefoot. Although there was little change in the size of the first negative phase of the responses in the cuneate nucleus between records 8*A* and *F*, the second negative wave was larger in 8*F* and the whole response became less variable. It seems likely therefore either

that more cells were firing, or that they were firing more often and with less variable latency when the anaesthesia was light. Little change in latency of the cuneate responses occurred with the change in anaesthetic level.

Duration of the effects of antecedent stimulation. The effect of stimulation of the cerebral cortex on subsequent mass responses of the cuneate nucleus to forefoot stimulation became very small 10 msec after the last cortical stimulus, though, as has been shown in the records in Fig. 3, the firing of some units could be inhibited for 40 msec or more by the cortical stimuli.

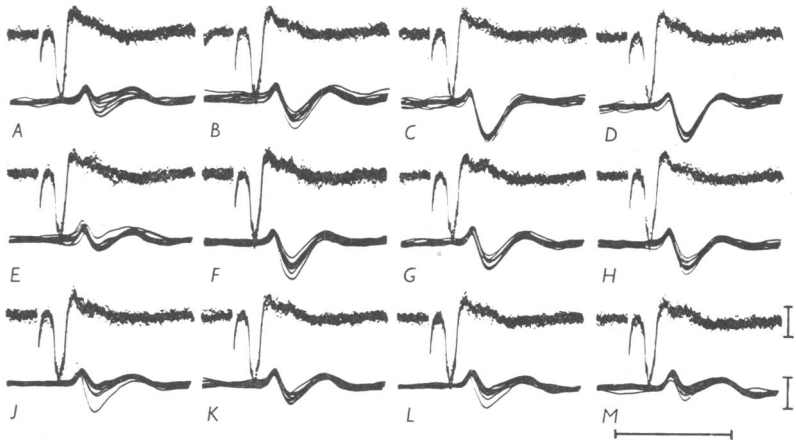

Fig. 9. The records show the right cuneate (above) and left cortical (below) responses to 10 successive stimuli to the right forefoot. In *A*, *E* and *J* the forefoot stimuli alone were applied. In the remaining records the test stimuli were preceded by a train of 30 stimuli at 3 msec intervals applied to the right hind foot. The interval between the last stimulus of the train and the test stimulus was, in record *B* 5, in *C* 105, *D* 205, *F* 305, *G* 405, *H* 505, *K* 605, *L* 705 and *M* 805 msec. The facilitatory effect is largest at 105 msec and still present at 605 msec. No change occurs in the size of the cuneate responses. The upper calibration in *M* shows 400 μV for the medullary responses and the lower 200 μV for the cortical responses. The time calibration shows 20 msec.

In contrast to these relatively short-duration effects of cortical stimulation on the responses of the nucleus, the increase in the cortical responses which was produced by stimulating the body surface lasted over 500 msec. A series of records of the test responses to stimulation of the right forefoot is shown in Fig. 9. Records *A*, *E* and *J* show ten responses to stimulation of the forefoot alone, with no antecedent stimulation elsewhere. In the other records the test stimuli were preceded by a train of 30 stimuli at 3 msec intervals applied to the left hind foot. The interval between the last stimulus of the train and the succeeding test stimulus was varied from 5 msec in *B* to 805 msec in *M*. The effect of the antecedent stimuli was considerable at

5 msec, greatest at 105 msec in *C*, and persisted clearly up to 605 msec in *K*. When the stimuli were separated by 805 msec in *M* the effect of the antecedent hind foot stimulation had largely worn off by the time the test response occurred. In none of these records was there any considerable alteration of the responses in the cuneate nucleus.

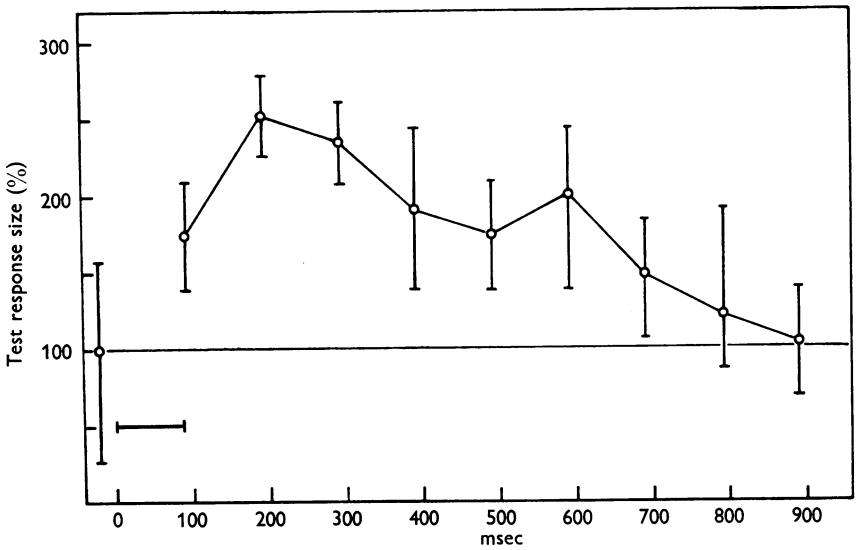

Fig. 10. The graph shows the relation between the amplitude, from the positive first peak to the negative trough following it, of the sets of 10 cortical responses in Fig. 9, and the interval between the start of the conditioning stimuli and the subsequent test stimuli. The circles mark the mean amplitudes and the vertical bars show the limits of scatter of the responses. The horizontal line shows the timing of the conditioning stimuli. The left hand vertical bar, plotted at a mean amplitude of 100, shows the unconditioned state.

The mean peak-to-peak size of the test responses has been plotted in Fig. 10, as a percentage of the size of the responses to the test stimuli alone, for different stimulus intervals. No data were available from this experiment for the interval between 5 and 105 msec and it is not clear whether the maximum effect of the hind foot stimulation occurred before 100 msec, though other experiments suggest that it does not do so. The vertical bars through the mean points indicate the extreme limits of scatter of the response size and show that the variation in size was least when the responses were most facilitated.

In view of the increase of the cortical response with lightening anaesthesia, an attempt was made to see if there was any evidence that the hind-foot stimuli were effectively changing the cortex from a deep to a lighter level of anaesthesia. A continuous electrocorticogram was taken

during periods when the test stimuli were being applied alone to the forefoot and also when they were preceded by stimulation of the hind foot. Two sets of such records are shown in Fig. 11. The upper pair of corticograms, *D* and *E*, show the type of activity recorded from near the primary somatic receiving area while the forefoot alone was stimulated. The time of stimulation is shown by the vertical mark in the time scale. In *A* are shown, superimposed and on a faster time base, the 10 responses from which the pair in *D* and *E* were taken. The corticograms in *F* and *G* were taken at the same time as the set of 10 responses shown superimposed in *B*, which were recorded during antecedent stimulation of the hind foot for the period indicated by the horizontal bar in the time scale. The antecedent

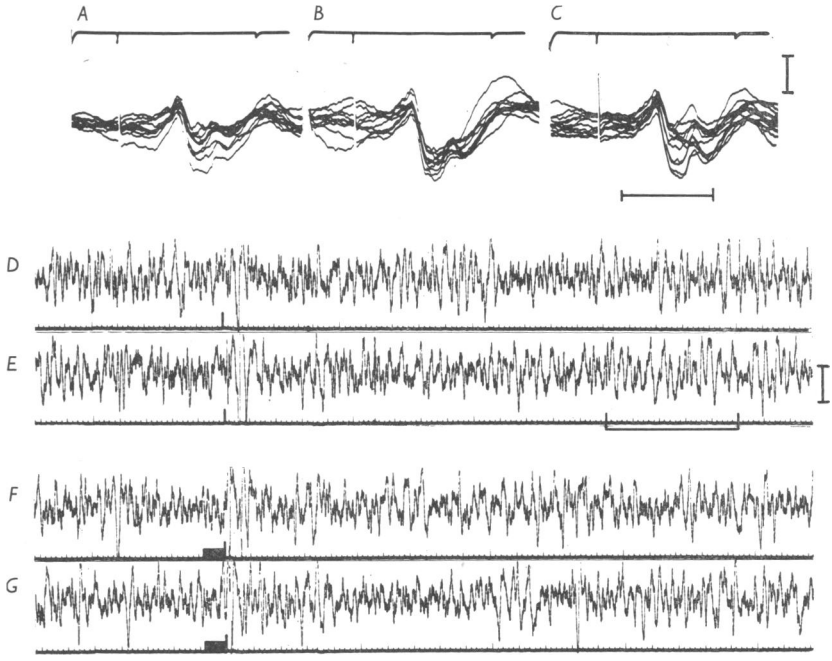

Fig. 11. In *A*, *B* and *C* are shown sets of 10 responses in the left sensory cortex to stimulation of the right forefoot once every 3 sec. In *B* the forefoot stimulus was preceded by a train of 30 stimuli at 3 msec intervals to the right hind foot, the last 5 msec before the test stimuli. *D* and *E* are continuous records covering two responses of the set in *A* and recorded from the same cortical electrodes. *F* and *G* cover two responses from the set of 10 in *B*. Though the responses in *B* were facilitated, records *F* and *G* did not show any great desynchronization of the spontaneous cortical rhythms during the period of facilitation. The timing of the forefoot stimuli in the continuous records is shown by the vertical line in the time scale and of the conditioning stimuli to the hind foot by the block before it. The calibration bar at the end of *C* shows 200 μV, and the bar below it 10 msec. The calibration at the end of *E* shows 100 μV for the corticograms and the bar below it 0·5 sec.

stimulation produced no gross reduction in amplitude of the spontaneous cortical activity, though it was sufficient to produce an increase in the negative second phase of the cortical response (Fig. 11*B*).

Pathway mediating the facilitatory effect

If the recording electrodes were placed on the cortical receiving area for a hind leg, a stimulus to the foot, insufficient to cause any muscular twitching, gave rise to a large response in the cortex. This response was abolished when the spinal cord in the lower thoracic region was cut halfway through on the side to which the stimulus was applied. The response was not abolished if the cord was cut half through on the side opposite to the stimulus. It therefore seemed that the cortical responses to stimuli below threshold for motor effects were mediated in the spinal cord by an uncrossed pathway. It was likely that this was the dorsal column pathway, but attempts to cut the dorsal columns on one side, without damaging any structures lying ventral to them, were not sufficiently satisfactory to demonstrate this clearly.

The strength of conditioning stimulus needed to facilitate the response to a test stimulus, when both were applied to the forefoot, was usually of the order of twice the threshold for twitching in the foot; it was therefore considerably stronger than that needed to produce a large direct response in the cortical receiving area for the part stimulated. On the other hand, the facilitating stimulus did not have to be increased any further when it was applied to a part remote from the site of the test stimulus; it was as effective on the face as on the hind foot of either side. When the facilitating stimulus was applied to a hind foot, hemisection of the spinal cord in the lower thoracic region on the same side did not prevent facilitation of the responses to a forefoot stimulus. Hemisection of the cord on the side opposite to the hind foot prevented the facilitation. It therefore seemed that the facilitating effect was mediated by a pathway which crosses shortly after entering the spinal cord and which has a higher threshold in its peripheral parts than the pathway mediating the direct responses.

DISCUSSION

Some caution must be exercised in using the mass response of the cuneate nucleus as a measure of the transmission of information in the sensory pathway. In normal function the number of post-synaptic elements discharging in a nucleus, and the pattern in which they discharge, are not uniquely related to the size or form of the mass response to a single electrical stimulus applied to the presynaptic elements. However, from the experiments described in this paper two things can be seen. In

the first place the size of the mass response in the cuneate nucleus bears a close relation to the strength of the peripheral stimulus between threshold and maximum values. Secondly, the size of the cortical mass response is related both to the strength of the stimulus and to the size of the cuneate response. It seems likely, therefore, that in the conditions of these experiments the size of the ascending volley above the nucleus, or its degree of synchrony, was related to the size of the mass response in the nucleus. It is therefore a useful indication of alterations in the state of the nucleus.

Stimulation of the cerebral cortex was found to affect the state of the cuneate nucleus in two ways. It could depress the size of the mass response to an electrical test stimulus applied to a forefoot, and it could arrest completely the activity of some single units in the nucleus. These units could also be arrested by electrical stimulation of large parts of the forelimb from which they were not excited. They were therefore probably similar to the type of unit found by Gordon & Paine (1960) in the nucleus gracilis of the cat, which had a small receptive field and could be relatively easily inhibited by stimuli elsewhere, or to the units described by Amassian & De Vito (1957). An arrest of activity in such units is not evidence for an inhibitory pathway from cortex directly to the nucleus, until it is known that the stimulus to the cortex is not giving rise to an afferent discharge from the periphery to the nucleus. No direct proof of this is available, but two findings in the present experiments suggest that the depression of the mass response was not due to an ascending discharge. In the first place, the minimum strength of cortical stimulus needed to depress the cuneate response did not produce in the forelimb any muscular movement which could be detected under a microscope. Secondly, the effect on the nucleus could begin 3 msec after a single electrical stimulus to the cortex. This would leave little time for a transfer from a down-going to an up-going pathway, peripheral to the nucleus, unless it was occurring practically at the level of the nucleus. The pathway is probably a simple one, since it would respond to several hundred stimuli per second under anaesthesia, and it may correspond to the anatomical findings of Walberg (1957).

In the earlier experiments it was thought that the cortical stimulus was taking effect under the cathode, which was over the primary somatic sensory area. But since the down-going elements could be excited by a single short shock, and showed no obvious after-discharge when stimulated repetitively at 3 msec intervals, it seems more likely that they were being directly excited under the anode, in the manner described by Hern, Landgren, Phillips & Porter (1962). If this was so, the position of the cortical stimulating electrodes with respect to the sensory cortex was evidently not critical, and the origin of the connexions responsible for the

down-going inhibitory effects was probably not restricted to the somatic receiving area. No evidence is available from these experiments to show if more inhibitory fibres originate in one part of the cortex than in any others.

In the small number of units sampled none was found which lay clearly in the main mass of the cuneate nucleus and which could be fired by cortical stimulation. Units were found which could be fired by the cortical stimulus with a latency of a few milliseconds, but they lay mostly in a region deep to the nucleus, though a few lay at an intermediate level which could have been in the deepest part of the nucleus. The failure to find units clearly in the nucleus which could be excited by cortical stimulation, like those described by Jabbur & Towe (1961), may reflect either the small number of units sampled or the conditions of anaesthesia. The fact that the mass responses were always reduced in size by cortical stimulation suggests either that inhibitory effects on the nucleus are more prominent than the excitatory ones, or that they are more direct and resistant to the anaesthesia used. At the same depth of anaesthesia, however, stimuli applied to any part of the body surface, and evidently acting through less direct pathways, had a large and long-lasting effect on the cortical responses.

When stimulation of the body surface affected the cortical responses to a forefoot test stimulus, the effect was always facilitatory. Although the antecedent stimulus applied to the body surface was considerably stronger than the test stimulus, no sign was found of the inhibitory effects described by Hernández-Peón, Guzmán-Flores, Alcaraz & Fernández-Guardiola (1957) in unanaesthetized animals with stimuli in different sensory modalities. In this respect our results are more comparable with those of Bremer & Stoupel (1959), who found that they could increase the responses of the optic cortex in the cat to stimulation of the optic nerve by stimulating the reticular formation. How far the increase in the cortical responses we have recorded was due to increased activity in the reticular formation is not clear, but if there was such an increase it was not associated with any considerable reduction or alteration of the continuous cortical potentials. It seems, therefore, that the responsiveness of the cortex to a single test stimulus in the periphery may be a more sensitive indication of the state of the cortex than is the level and type of its spontaneous activity.

The pathway through which the peripheral stimuli affect the cortical responses crosses to the opposite side soon after entering the spinal cord. It is not clear how the impulses in this pathway become generalized so that, no matter where the stimuli are applied, they can affect the responses to a forelimb stimulus. In the conditions of our experiments little or none of this alteration occurs in the cuneate nucleus. Evidence to be presented in the following paper (Angel & Dawson, 1963) shows that one site of

action, at least, is in the nucleus of the thalamus where the specific sensory afferent fibres relay on their way to the cerebral cortex.

SUMMARY

1. During anaesthesia with trichloroethylene the mass response in the cuneate nucleus to a single electrical stimulus on a forefoot was recorded. This response could be reduced, but was never increased, by preceding electrical stimulation of the contralateral cerebral cortex.

2. The effect of cortical stimulation on the cuneate mass response lasted for 10 msec after the last stimulus of a train at 3 msec intervals. It was apparently mediated by a pathway which could respond under anaesthesia to several hundred stimuli per second.

3. Single units and small groups of units were found in the cuneate nucleus, made active by mechanical stimuli in the periphery, which could be arrested completely for 40 msec by cortical stimulation and for up to 70 msec by peripheral electrical stimuli.

4. The responses to single electrical stimuli applied to a forefoot were recorded simultaneously from the ipsilateral cuneate nucleus and the contralateral primary somatic sensory cortex. These responses had a low threshold and a short latency.

5. At some levels of anaesthesia preceding electrical stimulation of any part of the body surface was found greatly to increase the second, negative-going, phase of the cortical response to a forefoot stimulus. No significant increase in the cuneate responses was seen while the cortical responses were increased. The cortical responses could be increased when the cuneate responses were diminished.

6. It is concluded that the facilitating stimuli operate through a pathway which decussates shortly after entering the spinal cord, and that they have their effect on the sensory inflow from the forefoot at a level above the cuneate nucleus. Under anaesthesia the pathway from cortex to the cuneate nucleus appears to be mainly inhibitory and plays no part in the facilitatory effects.

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