J. Physiol. (1964), **174**, *pp.* 370–399
With 18 *text-figures*
Printed in Great Britain

THE VENTRO-BASAL COMPLEX OF THE THALAMUS: TYPES OF CELLS, THEIR RESPONSES AND THEIR FUNCTIONAL ORGANIZATION

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(*Received* 11 *April* 1964)

Volleys in cutaneous nerves and afferent impulses initiated by tactile and joint-stimulation produce potential changes and also evoke the discharge of impulses in a quite sharply demarcated region of the contralateral thalamus, which is virtually coextensive with the ventro-basal complex (VBC) (Mountcastle & Henneman, 1949, 1952; Rose & Mountcastle, 1952; Poggio & Mountcastle, 1963). There have been extensive investigations of the activation of these VBC cells, as they will henceforth be called, by various forms of peripheral stimulation, and in particular Rose & Mountcastle (1954) studied with great detail and precision the repetitive spike discharges that are evoked by single volleys in cutaneous nerves: for example, the effect of variations in volley size on the number and frequency of the constituent impulses of the response, and also an analysis of the inter-spike intervals. Poggio & Mountcastle (1963) paid particular attention to the location, modality responsiveness and topographic organization of the individual VBC cells. On the basis of the dynamic properties, particularly the relation between stimulus frequency and response frequency, they reached the conclusion that virtually all VBC cells belong to a single uniform class, which is characterized by the fidelity of response to rapid repetitive stimulation of afferent nerves, there being on the average frequency following up to 100–120 sec.

Purpura & Cohen (1962) and Purpura & Shofer (1963) very successfully employed intracellular recording in order to analyse the responses evoked by stimulation of the mid-line thalamic nuclear complex. They demonstrated for the first time the large and prolonged post-synaptic inhibitory potentials of cells of the nucleus ventralis anterior, and the influence of these powerful inhibitions on spontaneous and evoked discharges. They

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postulated that this inhibition was the major factor in producing the temporal pattern of bursts of repetitive responses that was evoked by stimulation of the centre median.

The present paper gives an account of investigations on the VBC cells. Their responses were evoked by the different stimuli that were provided either by cutaneous afferent volleys or by stimulation of the somato-sensory cortex. Both extracellular and intracellular recordings were employed in the attempt to analyse the complex responses of the VBC cells, particularly their rhythmic burst discharges. The ultimate objective was to define the inhibitory pathways, to identify their constituent interneurones and to distinguish them from the thalamo-cortical relay cells. There have been preliminary publications of some parts of these investigations (Andersen & Eccles, 1962; Andersen, Brooks & Eccles, 1964). The experimental procedures have been fully reported in the preceding paper (Andersen, Brooks, Eccles & Sears, 1964).

RESULTS

Thalamo-cortical relay cells

Spike responses. In our identification of a thalamo-cortical relay (TCR) cell the only valid criteria were, conjointly, that the thalamic cell must be fired by a volley from an afferent nerve and that it must be invaded antidromically when the somato-sensory cortex is stimulated. In our standard procedure of testing for antidromic invasion, the bipolar stimulating electrode with about 2 mm interpolar distance was applied to the SI somato-sensory arm area. Of course, this definitive identification applies only in the positive sense; TCR cells may fail to qualify because the appropriate afferent nerve was not available for stimulation, or because the cortical stimulus failed to excite their axonal terminals.

Figure 1*A*, *B* gives an example of identification responses: the orthodromic spike potential set up at 3·5 msec after the arrival of the dorsal column volley at the cuneate nucleus in *A*, and the antidromic spike potential at 0·5 msec after the cortical stimulus in *B*. The antidromic spike appears to have a double composition comparable with the IS–SD spike of motoneurones, which may be observed extracellularly (Fatt, 1957) as well as intracellularly (Brock, Coombs & Eccles, 1953). For example, in the threshold-straddling series of cortical stimulation (Fig. 1*D*), the double spike with an interval of 0·2 msec appeared in an all-or-none manner superimposed on the stimulus artifact in three out of the eight superimposed traces, while with a stronger cortical stimulus there was invariably a double spike (*C*). Double cortical stimulation in *C–H* shows all stages in the recovery from refractoriness of the two components: at 1·24 msec

(*E*) there was refractoriness of both, possibly owing to the failure to set up an antidromic impulse; the interval of 1·36 msec (*F*) was just critical for production of the first component; at a testing interval of 1·75 msec (*G*, *H*) the first component was always evoked, but the second behaved in an all-or-none manner, arising at about 0·4 msec after the first in *H*.

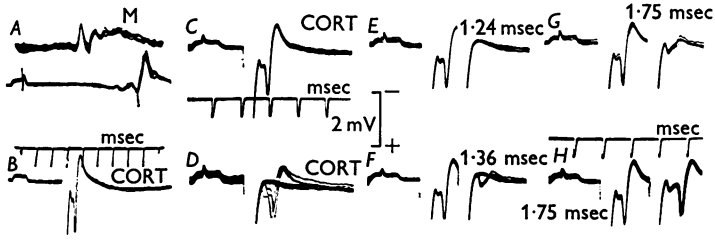

Fig. 1. Responses of a thalamo-cortical relay cell. The spike potentials were recorded extracellularly by a micro-electrode in the ventro-basal complex. *A* and *B* show spikes recorded at same amplification and sweep speed, and evoked orthodromically (*A*) by a contralateral median nerve volley and antidromically (*B*) by a stimulus to the ipsilateral somato-sensory cortex. In *A* the upper trace is from the surface of the contralateral cuneate nucleus. *C* and *D* are antidromic responses at faster sweep speed, the cortical stimulus in *D* being just on threshold. *E–H* give responses to two cortical stimuli applied through the same electrodes at the indicated intervals. Same amplification for all thalamic records. All records formed by the superposition of several traces.

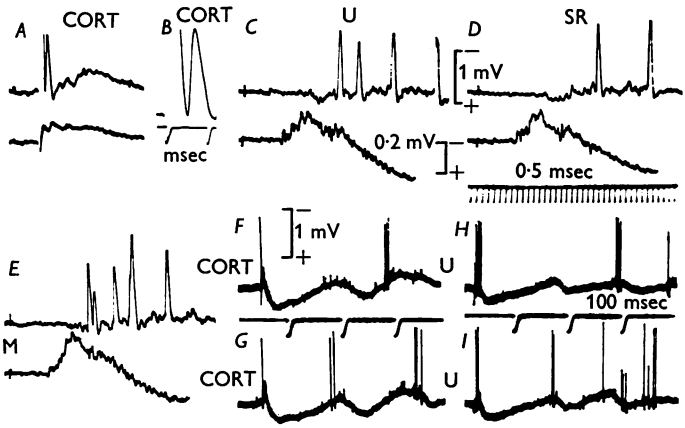

Fig. 2. Responses of a thalamo-cortical relay cell. *A*, *B* show at two sweep speeds antidromic spike potentials extracellularly recorded in the ventro-basal complex and evoked from the ipsilateral somato-sensory cortex. *C*, *D*, *E* are orthodromic responses to contralateral U, SR and M volleys. In *A*, *C–E* the lower traces are from the surface of the contralateral cuneate nucleus, and all are at the same speed (below *D*) and amplification (above *F*). *F–I* are thalamic potentials evoked from the sources specified and similarly recorded at same amplification, but at much slower sweep speed.

This IS–SD configuration of the antidromic spike potential was not observed with all TCR cells (cf. Figs. 2*B*, 3). Possibly the interval between the two components may be too brief for detection by our relatively crude recording procedures; alternatively, if the extracellular recording is from dendrites, the very small initial IS component may escape recognition. A trace of this double IS–SD configuration can also be seen in the orthodromically evoked spikes in Fig. 1*A*, and has previously been reported by Rose & Mountcastle (1954), and by Purpura & Cohen (1962).

The antidromic responses of the TCR cell in Fig. 2*A*, *B* show a single spike response with a latency of 0·55 msec and a total duration of 0·6 msec. Each of the three afferent volleys evoked a repetitive discharge of this cell (*C–E*), the respective latencies of the first discharges being 4·85, 7·35 and 3·6 msec after arrival of the dorsal column volley in the cuneate nucleus. Probably the SR response (*D*) had a long latency because it was not produced directly by the SR volley, but only secondarily thereto by the dorsal root reflexes or dorsal column reflexes that the SR volley generated in M or U afferent fibres (Andersen, Eccles, Schmidt & Yokota, 1964). A similar explanation may also account for the last two spike responses in *C* and *E*. The small spike response of a second cell provided a further complication in *E*, where the fourth, very large, spike can be seen to be due to superposition of the two spikes. The slower records of *F–I* illustrate the way in which spike potentials tend to occur on the negative components of the rhythmic waves, so contributing to the burst discharges. Nevertheless, there was a considerable degree of variation between successive responses to the same initial stimulus, either to the cortical stimulus in *F* and *G* or to an ulnar afferent volley in *H* and *I*; and the increasing asynchronism of spikes with negative waves doubtless contributes to the progressive deterioration of the rhythmic wave (cf. Andersen, Brooks, Eccles & Sears, 1964).

In applying the criterion of antidromic invasion from the cortical stimulation, it must be recognized that often the antidromic impulse in a thalamo-cortical fibre fails to invade the thalamic cell unless this is appropriately conditioned by depolarization. In the superposed traces of Fig. 3*I* only one of about fifteen cortical stimuli resulted in an antidromic spike potential. However, if the cortical stimuli were applied during synaptic excitation of this cell by an SR afferent volley, an antidromic spike potential could invariably be produced. The optimal conditions for antidromic invasion occurred in Fig. 3*D*, *E* where the antidromic impulse reached the cell before the synaptic excitation had caused it to fire impulses. The latency of the antidromic spike was then 0·6 msec. In Fig. 3*A–C* there is seen to be progressive improvement of antidromic invasion as the antidromic impulse reached the thalamic cell later and later during

the build up of synaptic excitation by the SR volley. In Fig. 3*F*, *G* antidromic invasion was depressed on account of refractoriness owing to synaptically generated spikes, but in *H* there was again a regular anti-

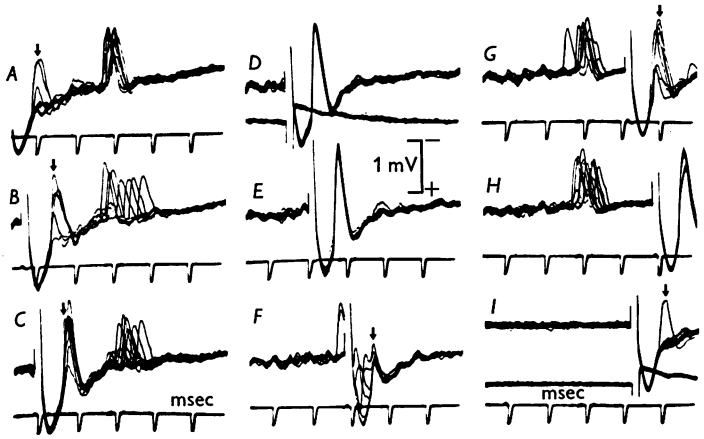

Fig. 3. Facilitation of antidromic invasion of thalamo-cortical relay cell. As described in text, antidromic invasion rarely occurs (*I*) unless conditioned by a depolarization that in *A–H* is produced by a contralateral SR volley. In *A–H* the SR volley is set up at a fixed time relative to the sweeps and the cortical stimulus is applied progressively later in the sweep as shown. All records are formed by the superposition of about ten faint traces.

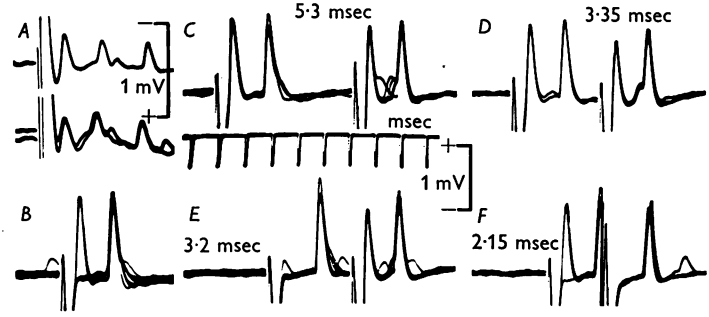

Fig. 4. Antidromic and orthodromic activation of thalamo-cortical relay by subcortical stimulation. In *A* and *B* single stimuli were applied to the white matter exposed after removal of the ipsilateral somato-sensory cortex by suction. In *C–F* there was double stimulation through the same electrodes. After the extracellular records of *A*, the micro-electrode partly impaled the cell as shown by the reversed potentials in *B–F* (note the respective voltage scales). Further description in text. All records are formed by the superposition of about five faint traces.

dromic invasion of the cell, which was presumably due to residual synaptic excitation. The irregularity of size and configuration of the synaptically evoked spikes in Fig. 3*G*, *H* indicates that impulse propagation over the

cell was not an all-or-nothing phenomenon; and this is also seen where antidromic invasion was not fully facilitated as in *B*, *C*, *F* and *G*. In part this variability in spike response appears to be due to the double IS–SD composition of the spike. The latency of the synaptically induced spike response was as brief as 4·2 msec after the arrival of the SR volley at the cuneate nucleus; and U and M volleys also initiated spikes at about this same latency, 4·0 and 3·8 msec, respectively, there being a double spike response (1·2 msec interval) to the M volley.

A cortical stimulus often evoked in the thalamus traces of spike potentials that appeared to follow repetitively the initial antidromic spike potential (see Fig. 2*A*). In Fig. 4*A* the single and the two superimposed traces all show the same triple spike response of unitary character, the inter-spike intervals being 1·4 and 1·7 msec, respectively. Later this same thalamic cell gave only the double spike response of Fig. 4*B*, where the initial antidromic spike (latency 0·7 msec) sometimes failed (as in Fig. 3*I*).

Fig. 4*C–F* gives examples of responses to two cortical stimuli at the indicated intervals. Rigorous interpretation of these responses is not possible because of the variability of the antidromic invasion. However, this invasion invariably occurred to the second cortical stimulus at 3·2, 3·35 and 5·3 msec, the failure at 2·15 msec being attributable to refractoriness following the second spike response evoked by the first stimulus. Another point of interest is that the second conditioned response in *C*, *D*, *E* can be seen to arise from a preliminary small depolarization or prepotential. Since the cortical stimuli in Fig. 4 were applied to the underlying white matter after removal of an extensive area of grey matter by suction, and so were strictly subcortical, it must be concluded that the second responses in Fig. 4 were generated in the thalamus. This could conceivably be due to the synaptic excitatory action of a cortico-thalamic pathway. A simpler alternative is that the excitation of thalamic cells occurs through axon collaterals from the thalamo-cortical fibres, which would be an example of positive feed-back. Since the second response of the thalamic cell in Fig. 4 was produced even by a subcortical stimulus below threshold for antidromic activation of that cell, it would have to be postulated that the excitation was produced by recurrent collaterals of other thalamo-cortical relay cells. Figure 7 shows other examples of the effectiveness of cortical stimulation in generating spike potentials after the initial antidromic spike.

Inhibitory and facilitatory action on impulse discharges. Following the response evoked in the somato-sensory cortex by an afferent volley there is a prolonged depression of the response produced by a second volley either in the same or another nerve (Marshall, 1941; Andersen, Brooks,

Eccles & Sears, 1964). For example, in the lower traces of the specimen records of Fig. 5 there was virtually no cortical response to an SR volley at 15 msec after the combined conditioning U + M volleys, and at 33 and 60 msec the response was small. As would be expected, this depressed transmission to the cortex was paralleled by the reduced discharges of individual thalamo-cortical relay cells; in Fig. 5 (upper traces) it can be seen that the cell that gave two discharges in the control response gave

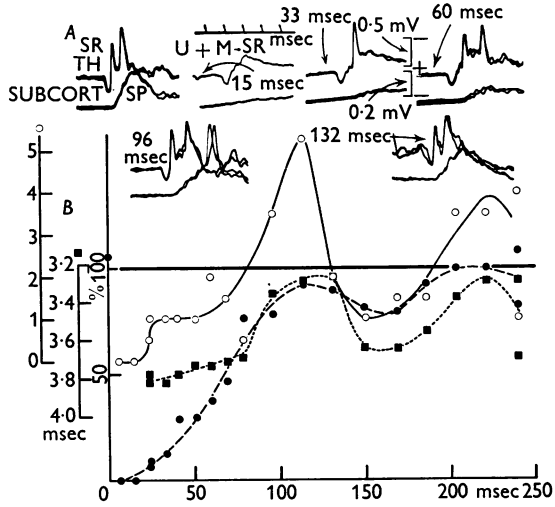

Fig. 5. Inhibition and facilitation of a thalamo-cortical relay cell. *A*. The control specimen record evoked by a contralateral SR volley shows a double spike discharge of a TCR cell (TH) and a slightly later positive wave (SP) with 'killed-end' recording (SUBCORT) from the white matter exposed by removal of the somatosensory cortex. In the other specimen records the SR response was conditioned by a preceding U plus M volley at the indicated intervals. Note separate potential scales for the thalamic and subcortical records. *B*. In the plotted curves measurements from the whole series of responses (partly illustrated) are plotted against the conditioning-testing intervals. Note separate ordinate scales for spike number, spike latency and the size of the subcortical positive spike (SP). The mean control values for each of these three measurements are given by the horizontal line. ○, spike number; ●, SP-wave, SUBCORT; ■, spike latency.

none at 15 msec, and one at 33 msec. However, at intervals around 100 msec, the testing volley was superimposed on the increased excitability that was responsible for the first burst discharge; consequently the number of spike discharges was increased to three at 96 msec and even more at 114 msec, as may be seen in the plotted points of Fig. 5. Thereafter the depression was re-imposed during the P-wave that followed the first burst discharge, but increased excitability again occurred during the second burst discharge at about 200 msec. In Fig. 5 the latency of the first dis-

charge of the unit spikes also gave an index of the initial inhibition and of the intercurrent excitations and inhibitions due to burst discharges. Curves for single unit responses of rat thalamus resembling in general those of Fig. 5 have been illustrated by Angel & Dawson (1963).

The inhibitory action of an afferent nerve is also displayed by the suppression of the spontaneous discharges of thalamic relay cells. The two thalamic relay cells in Fig. 6 were fired by SR and M (*A*, *B*) volleys and not by U (*C*). However, in *D–F* it is seen that all three nerve volleys

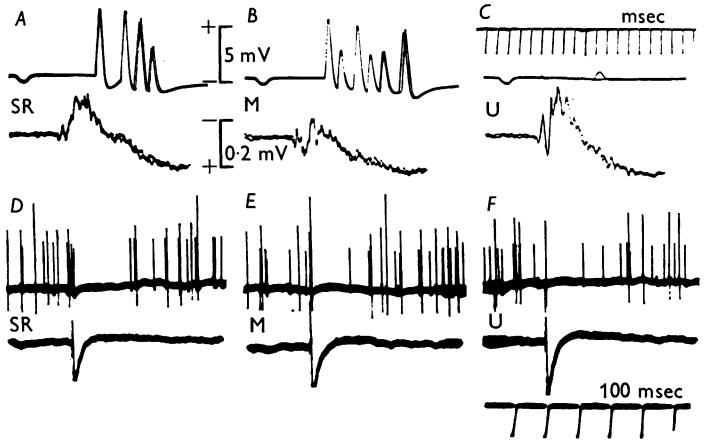

Fig. 6. Inhibition of spontaneous discharge of thalamo-cortical relay cells by a contralateral afferent volley. Specimen records to SR, M and U volleys show that only the first two evoked discharges from the two TCR cells; yet in *D–F* each of the three volleys caused a prolonged cessation of the spontaneous firing of these cells. Note much slower sweep speed for *D–F*, but same voltage scales. Two traces are superposed in *A–C*; *D–E* are single traces.

caused a prolonged suppression (120–180 msec) of the spontaneous discharge of at least three cells including the two in *A* and *B*.

Figure 2*F–I* shows that often a cell fires repetitively in a brief burst during each of the waves of relative negativity that alternate with the rhythmic P-waves (cf. Andersen, Brooks, Eccles & Sears, 1964). Two possible explanations of these repetitive bursts can be suggested: one is simply that the cell discharge is due to a prolonged excitatory synaptic action which generates several spikes in quick succession; the other is that the first discharge initiates some self re-exciting mechanism. This latter explanation satisfactorily accounts for the burst discharges prematurely initiated by cortical stimulation in Fig. 7*G–J*.

In Fig. 7 the first burst discharge to a conditioning SR volley is shown at a slow sweep speed (*C*, *E*), and also at a fast sweep speed (*A*), where it is seen to comprise four unitary spikes at about 500/sec. The first burst

was remarkably constant during the series of responses from which those of Fig. 7 were selected. In the six control responses, of which two (*C* and *E*) are illustrated, the average latency of the burst was 137 msec (range

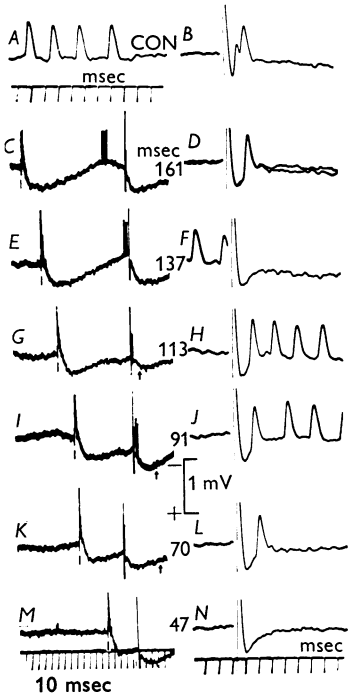

Fig. 7. Relation of cortical stimulation to the processes producing burst discharges from thalamo-cortical relay cells. In the series of records *C–N*, the left-hand traces show the relation of a testing subcortical stimulus (the somato-sensory cortex having been removed) to the thalamic response evoked by a contralateral SR volley, while the right-hand traces are fast sweeps in order to give details of the responses evoked by the subcortical stimulus. The millisecond intervals between the two columns give for each pair of responses the interval by which the SR stimulus precedes the subcortical stimulus, e.g. SR 161 msec SUBCORT for *C* and *D*. *A* and *B* show respectively the first burst discharge and the control antidromic response at this same fast sweep. As described in the text, the first burst discharge normally occurred at a fairly constant time, the earliest observed time for six control observations being marked by arrows in *G*, *I* and *K*. For this purpose observations such as *C* and *E* serve as controls, the first burst discharge preceding the subcortical stimulus.

129–145) and it comprised on the average four spikes (range 3–5). Figure 7 *B* shows that cortical stimulation evoked a double spike response resembling that in Fig. 1. When this cortical stimulus was applied at the indicated intervals following the conditioning SR volley, the slow (*C*, *E*, *G*, *I*, *K* and *M*) and fast (*D*, *F*, *H*, *J*, *L* and *N*) sweep records of Fig. 7 were

obtained. It is of great significance that in *G* and *I* the cortical stimulus caused the repetitive burst to appear prematurely at latencies of 114 and 92 msec, respectively, i.e. the testing interval plus the one millisecond latency from stimulus to response. The corresponding fast records, *H* and *J*, show that the burst prematurely initiated by the cortical stimulus closely resembled the normal burst in *A*, except that in *J* the first interspike interval was longer. In Fig. 7*D*, *H*, *J* and *L*, the first component of the double spike response due to cortical stimulation was absent. The cortical stimulus at 70 msec (*K*, *L*) initiated only a single spike with a somewhat lengthened latency, and at the trough of the P-wave, 47 msec, (*M*, *N*) even that spike was suppressed. In *E* refractoriness due to the immediately preceding burst discharge accounts for the failure of an antidromic spike response, and during the second P-wave (*C*, *D*) the response resembled that at 70 msec (*K*, *L*).

This ability of the cortical stimulus to initiate a premature repetitive burst has also been observed with three other thalamic relay cells where the repetitive burst response was sufficiently stable. The interpretation of these results will be attempted in the Discussion.

Intracellular recording of synaptically induced potentials. The thalamic cells are relatively small and very readily injured by the impaling microelectrode. Prolonged conditions of stable recording were therefore rarely obtained, and the membrane potentials were so low that spike potentials were often depressed or absent. Nevertheless, intracellular recording has given much valuable information, particularly in relation to the mechanism governing the production of the burst discharges.

Though there are no controls of extracellular field potentials, the potential waves of Figs. 8 and 9 can be identified as hyperpolarizing when in the downward direction (increased intracellular negativity) and depolarizing when upward. The direction of recording is inverted with respect to the extracellular recording of thalamic potential waves in the preceding paper (Andersen, Brooks, Eccles & Sears, 1964); hence the extracellular field potentials would be opposite in sign to the intracellular, but much smaller in amplitude. Consequently, the changes in membrane potential would actually be a little larger than those observed in the records of Figs. 8 and 9. The lowest trace of Fig. 8*B* shows the transition almost to extracellular recording and illustrates that the large dominant deflexions in the two upper TH traces were genuine membrane hyperpolarizations.

In Fig. 9 the impaled cell is identified as a thalamo-cortical relay cell because it is synaptically excited to discharge an impulse by single M and U volleys (*A–C*), and is also antidromically activated after cortical stimulation (*E–G*). When first impaled (*A–C*), the large initial hyperpolarization following the spike was interrupted by a small wave of

relative depolarization with a summit at about 150 msec (see arrows) and then there was a larger later wave in *A–C* on which was superimposed a burst discharge in *B* and *C* at about 250 msec after the M and U volleys. With cortical stimulation in *D* the two depolarizing waves were of similar height, but somewhat later (*F*, *G*) the first wave was large with three unitary spikes superimposed (the fast record of *M*) and the second wave was small (*H–I*). These unitary spikes of the first burst response are seen in *M* to be identical with the antidromic spike produced by a cortical

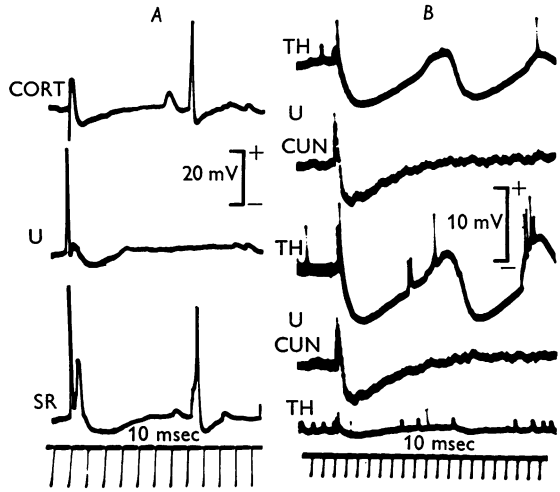

Fig. 8. Intracellular responses of thalamo-cortical relay cells. In *A* the membrane potential was about −60 mV and contralateral U and SR volleys set up large spike potentials and later IPSPs, whereas cortical stimulation evoked only a small initial depolarization and later IPSP. Two examples of burst discharges are seen. In *B* are two examples of effect of contralateral U volleys in evoking an initial EPSP and later rhythmic IPSPs with signs of burst discharges on the depolarizations between the successive IPSPs. The simultaneously recorded traces of CUN responses are seen below the TH traces. Lowest trace shows TH record when micro-electrode had virtually moved to an extracellular position.

stimulus at the arrow about 15 msec later. In *J–L* and *N–P* this cortical stimulus was applied at progressively shorter intervals after the initial stimulus (arrows), *I* being the control response to one cortical stimulus alone. During the second wave of hyperpolarization (*J*, *K*), antidromic invasion failed and there was merely a small additional hyperpolarization. At *L* there was a small antidromic spike, indicating failure of invasion of most of the cell. In *N* the antidromic response was superimposed on the first burst response. At the still briefer intervals, *O* and *P*, antidromic invasion again failed during the first initial hyperpolarization, but just as in *J* and *K* an additional hyperpolarization was produced.

When the cortical stimulus failed to produce an antidromic spike potential, as occurred for the second stimulus in *J*, *K*, *O* and *P* (Fig. 9), the hyperpolarization must be synaptically induced, and be an example of an inhibitory post-synaptic potential (IPSP). It might be suspected that the initial spike response in Fig. 9, whether orthodromic (*A–C*) or antidromic (*E–L*, *N–P*), would be followed by an after-hyperpolarization, AHP, that would summate with the concurrent IPSP, much as occurs with the after-hyperpolarization and the recurrent IPSP of the motoneurones (Eccles, Fatt & Koketsu, 1954). However, it is seen in *G* that,

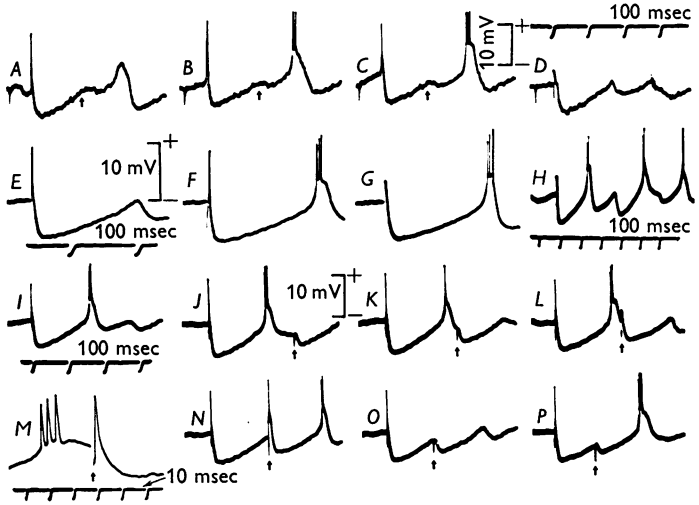

Fig. 9. Intracellular recording from a thalamo-cortical relay cell. The condition of recording improved after the initial series, *A–D*. Responses *A–C* were evoked by the contralateral M + U afferent volleys. Responses *D–P* were evoked by stimulation of the ipsilateral somato-sensory cortex. There was double stimulation in *J–L* and *N–P*, which were at the same sweep speed as *I*. *A–D* were at same sweep speed and amplification. *E–G* were at the sweep speed and amplification indicated for *E*. Independent sweep speeds are given for *H* and *M*, but *H–P* at same amplification. Further description in text.

when full antidromic invasion failed, the initial wave of hyperpolarization was still as large as in *E* and *F*, and this is also seen when *D* is compared to *A*, *B* and *C*. Other examples are given in Figs. 10 and 11, where orthodromic or antidromic volleys produced large initial hyperpolarizations in the absence of impulse generation. In fact there is no evidence that the spike potential of a thalamic relay cell is followed by any appreciable after-hyperpolarization, which is in agreement with Purpura & Cohen (1962).

Figure 9 gives excellent illustration of the way in which the burst dis-

charges are generated by slow waves of depolarization. In the slow record of *H* there were four successive waves of depolarization, three of which generated burst discharges. The mechanism of production of these rhythmically occurring depolarizations is considered in the Discussion. Figure 9*J–L* and *N–P* shows the way in which an intercurrent cortical stimulus interfered with the rhythmic depolarizations, which will also be considered in the Discussion.

Figure 9*A–C* shows that an orthodromic volley sets up an initial EPSP with superimposed spikes and a later IPSP. Graded afferent stimulation

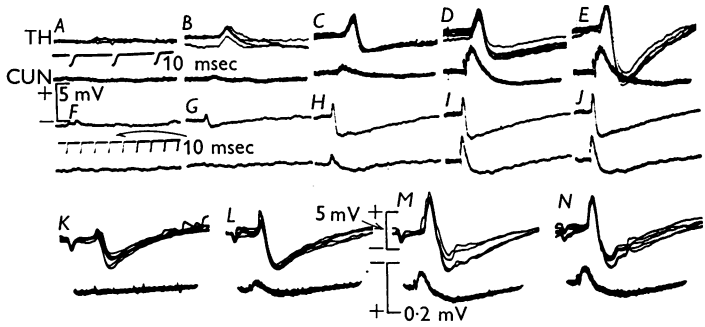

Fig. 10. Intracellular responses of thalamo-cortical relay cells to graded afferent volleys. Upper traces in *A–E* are intracellular potentials evoked by contralateral M volleys, *A* being the just-threshold response and *E* the maximum. Membrane potential −20 mV. Immediately below the TH traces are the corresponding traces (CUN) from the surface of the contralateral cuneate nucleus. *F–J* are the same series but at slower sweep speed. The voltage scale is for the TH records only. *K–N* are a similar series for U volleys in another experiment: note separate voltage scales for the TH and CUN traces. Same sweep speed as for *A–E*.

has been employed in attempting to discriminate between these dual actions. Just-threshold stimulation of the M nerve in Fig. 10*A*, *F*, appeared to evoke merely a small EPSP, but in *B* and *G* a slight increase resulted in a dual response, the EPSP being followed within 2 msec by an IPSP; and both became larger with further increase in the stimulus (*C*, *D* and *H*, *I*). With maximal stimulation (*E*), there was a further large increase of the IPSP. The slower traces of *F–J* illustrate the long duration (about 100 msec) of the IPSP. In a comparable series with graded stimulation in another experiment (Fig. 10*K–N*) it is seen that the IPSP was large (*K*) with a stimulus just above threshold.

In the preceding paper (Andersen, Brooks, Eccles & Sears, 1964) it was shown that repetitive stimulation could maintain and even develop a rhythmic burst discharge if the stimulation was at a frequency appropriate for resonance with the naturally occurring rhythm. Intracellular

recording gives evidence relating to the mechanism of this resonance. In Fig. 11*A*, *F*, a single cortical stimulus evoked an IPSP followed at 145 msec in *A* by a depolarization with superimposed spike discharge, then a second IPSP with an irregular phase of depolarization, followed by a third IPSP. In addition there were later small waves in the slower trace (*F*). In *D*, with repetitive cortical stimulation at 6·9/sec, the second stimulus arrived during the first burst discharge and sharpened the onset of the second IPSP, with the consequence that there was an augmented depolarization with superimposed burst discharge on which the third stimulus was

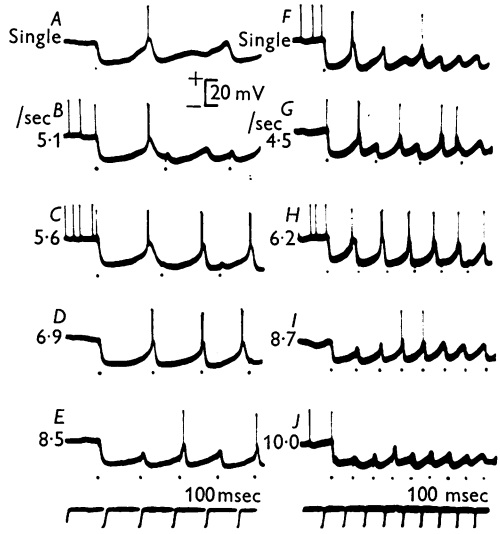

Fig. 11. Intracellular responses of thalamo-cortical relay cell to repetitive cortical stimulation. *B–E* are the responses of a TCR cell to repetitive stimulation of the somato-sensory cortex at the indicated frequencies, the times of the actual stimuli being indicated by dots. *G–J* are a similar series from the same TCR cell, but at a slower sweep speed. *A* and *F* show the respective rhythmic responses evoked by single cortical stimuli. d.c. amplification at the same gain was employed throughout.

superimposed. The subsequent third burst discharge occurred at a shorter interval, so moving out of phase with the repetitive cortical stimulus. Nevertheless, *C* and *H* show that, even when much later than the burst discharges, the IPSP added by the cortical stimulus was effective in augmenting and synchronizing the components of the next depolarization, with the consequent enhancement of the superimposed burst discharge. However, when too far out of phase (*B*, *G*), the cortical stimulus had no such adjuvant action. At the other extreme, too rapid a cortical stimulation (*E*, *I*, *J*) often prevented the depolarization from generating a burst

discharge, though its regular production of IPSPs caused the IPSPs and subsequent depolarizations to be strictly in phase; and this apparently would continue indefinitely in *I*. It will be noted that in Fig. 11 the cortical stimulus always gave effective antidromic invasion of the thalamic cell when it was discharging spontaneously, but otherwise only in record *G*. It will be noticed that in *E*, when the cortical stimulus forestalled the time of the first burst discharge by less than 30 msec, it failed to generate a burst discharge in the manner illustrated in Fig. 7*G–J*.

Figure 12 shows that, as with the IPSPs of other cells in the central nervous system, an increased conductance of the inhibitory subsynaptic membrane to chloride ions contributes to the generation of IPSPs (cf. Eccles, 1964, Chapt. XI). By chance, a coarse NaCl electrode (2·5 MΩ

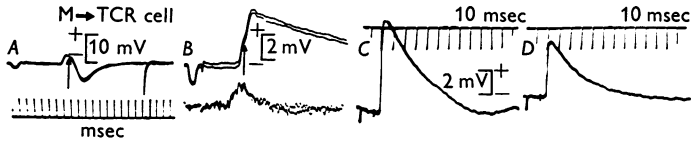

Fig. 12. Effect of increased intracellular chloride concentration on the IPSPs of a TCR cell. Immediately after impalement by a relatively coarse NaCl electrode the diphasic EPSP–IPSP response of *A* was recorded. Within a minute the response *B* shows that the IPSP had been inverted to a depolarizing response that arose from the initial EPSP at the inflexion signalled by the arrow. Note higher amplification, but same sweep speed. *C* and *D* show a further development of this depolarizing transformation of the IPSP taken at a much lower sweep speed, with an amplifier time constant in *D* of 1 sec.

resistance) that was being employed for extracellular recording impaled a thalamic relay cell, M-nerve stimulation producing an EPSP followed after about 1·3 msec by a brief hyperpolarizing IPSP (Fig. 12*A*). Within a minute this hyperpolarization had inverted to a depolarization separated from the original depolarization by an inflexion, the arrows in *A* and *B* indicating corresponding times. Record *C* shows the further development of this large depolarizing IPSP at a slower sweep speed, while at *D* the time course was more accurately displayed, the amplifier time constant being increased from 200 msec to 1 sec. Such inversion of IPSPs was regularly observed when the impaling micro-electrodes were filled with KCl or NaCl.

The pathway for post-synaptic inhibition

Afferent volleys produce an IPSP with such a short latency after the EPSP that it must be generated by some pathway containing no more than two or three synaptic relays. The cortical ablation experiments (Figs. 9, 11, 13; Andersen, Brooks, Eccles & Sears, 1964, Fig. 3) exclude a cortical link in the inhibitory pathway. The very similar IPSPs generated by

cortical stimulation, and the subsequent burst discharges, suggest that the same pathway is operated by this stimulation. It has been postulated (Andersen & Eccles, 1962) that this pathway is formed by axon collaterals of thalamo-cortical relay cells exciting inhibitory interneurones in the region of the ventro-basal complex of the thalamus and that their inhibitory synaptic action is widely distributed to the thalamo-cortical relay cells. The inhibitory action would thus be a typical example of recurrent inhibition as first defined in the inhibitory pathway through Renshaw cells to motoneurones in the spinal cord (Eccles *et al.* 1954). However, an

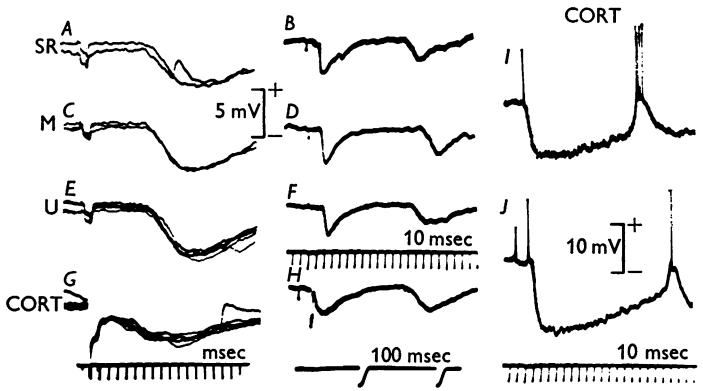

Fig. 13. Intracellular responses of thalamo-cortical relay cells to afferent volleys and to subcortical stimulation many days after ablation of the sensori-motor cortex. In *A–H* the sensori-motor cortex had been removed aseptically 12 days before. The intracellular responses of a TCR cell to contralateral nerve volleys and to ipsilateral subcortical stimulation are shown at fast and slow sweeps as indicated, and at same amplification, there being superposition of several traces with the fast speeds. *I, J* are intracellular responses evoked by subcortical stimulation in another TCR cell, and show the first burst response arising from a depolarization much as in Fig. 9. Same voltage scale as for *A–H*, but in another experiment also 12 days after ablation of the sensori-motor cortex.

alternative postulate could be that the cortically evoked inhibition is due to a pathway from cortical cells to the thalamus, for which experimental evidence has been provided by Iwama & Yamamoto (1961) and by Angel (1963), and not to antidromic activation of axon collaterals of the thalamo-cortical relay cells.

In thirteen experiments this alternative postulate was tested after operative ablation of the somato-sensory areas of the cortex and the subsequent degeneration of any axons of cortical cells that could project to the thalamus. As long as 12 days after the ablation there was typical production of IPSPs in a thalamo-cortical relay cell both by afferent volleys (Fig. 13*A–F*) and by stimulation of the white matter below the

excised cortex (Fig. 13*G*, *H*). Furthermore, with all these stimuli there is seen in *B*, *D*, *F*, *H* to be the typical rhythmic IPSP production. Since stimulation of the white matter was just as effective as afferent nerve volleys in producing the rhythmic IPSPs and superimposed burst discharges (Fig. 13*I*, *J*), the postulate of their projection by cortico-thalamic cells is not required. In these thirteen experiments the investigations were carried out at a time adequate for degeneration of axons severed from their cell bodies, but not long enough for the degeneration that occurs in thalamo-cortical relay cells when their cortical terminals are ablated (le Gros Clark & Powell, 1953).

The postulated cells on the post-synaptic inhibitory pathways

So far we have made only a preliminary attempt to discover the postulated inhibitory cells on the inhibitory pathway from the axon collaterals of thalamo-cortical relay cells. Such cells should be synaptically excited secondarily to any excitation of the thalamo-cortical relay cells, but never invaded directly by antidromic impulses generated by cortical stimulation. Further criteria possibly are that these cells should not themselves be subjected to inhibition from the post-synaptic inhibitory pathway, and that, when excited by afferent or antidromic volleys, they should often fire repetitively for 10 or more milliseconds to give the prolonged rise to the summit of the observed IPSP (cf. Figs. 8–13). In other respects, for example, the participation in the burst discharges, these postulated inhibitory cells would resemble the thalamo-cortical relay cells.

Figure 14 shows responses of the cell that best fulfilled these criteria in our total of 167 thalamic neurones. In *A* and *B*, the SR and U volleys evoked repetitive discharges starting at a latency of 5 msec from the arrival of the orthodromic volleys in the cuneate nucleus, which would be early enough for the observed onset of IPSPs (cf. Figs. 9, 10, 12, 13), and continuing for over 20 msec. As shown in Fig. 14*C*, *D*, the cortical stimulus generated a repetitive spike discharge with a latency of about 1·1 msec, and later inter-spike intervals of about 1·1, 1·9 and 2·1 msec which are shown in the superimposed traces of *D* to constitute a very reproducible repetitive response. The series of graded cortical stimuli in *E–H* is remarkable in showing a very long latency of 3·5 msec for the response to the just-threshold stimulus (*E*), and a progressive shortening of latency and increase of frequency as the stimulus was increased in *F–H*. Unfortunately, no slow records were taken to see if this cell participated in the rhythmic burst discharges. However, the tests for inhibition were of interest; an SR volley had no appreciable depressant action on the excitatory response to a cortical stimulus until the conditioning-testing interval was very short. There was a much more severe depression in the

reverse sequence, cortical stimulus preceding SR. This could be due to the cortically induced inhibition of thalamo-cortical relay cells (Andersen, Brooks, Eccles & Sears, 1964) with the consequent failure of activation by impulses in the axon collaterals. Since the cortical stimuli were applied to the white matter after removal of the somato-sensory cortex, the responses shown in Fig. 14 *C–H* must be attributed to a prolonged synaptic excitation of this thalamic cell by a single volley of impulses, which accords well with the postulate that the synaptic excitation is effected by antidromic impulses acting through the axon collaterals of thalamo-cortical relay cells.

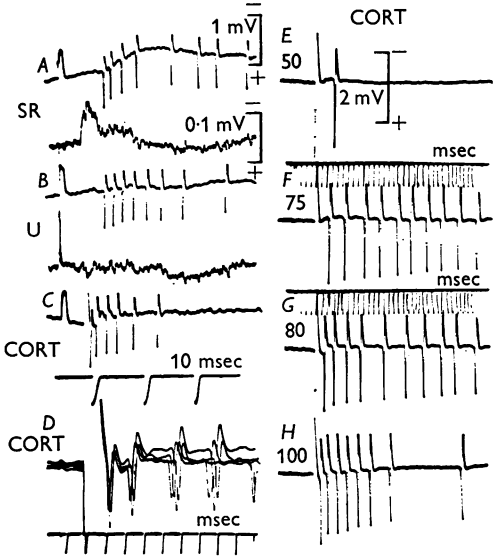

Fig. 14. Extracellular responses of a presumed post-synaptic inhibitory interneurone. Upper traces of *A*, *B* show repetitive spike responses to contralateral SR and U volleys, the lower traces being the respective potentials from the dorsum of the cuneate nucleus. *C* shows repetitive spike response to ipsilateral cortical stimulation at the same sweep speed, while in *D* are four superimposed traces to this same stimulus but at higher sweep speed. The voltage scale for thalamic records *A–D* is shown for upper trace of *A*, the cuneate scale being given on lower trace. In *E–H* are responses to cortical stimuli, the numbers giving relative strengths. Same voltage scale and sweep speed throughout.

In this same experiment there were less complete investigations on seven other cells that were possibly post-synaptic inhibitory relay cells. They were observed in two clusters, one including the cell shown in Fig. 14. Also in other experiments there were brief test series on eight thalamic cells that were not antidromically invaded, but were synaptically excited by cortical stimulation, and which in other respects also appeared to qualify as post-synaptic inhibitory relay cells.

The pathway for presynaptic inhibition

On analogy with the spinal cord (Eccles, Kostyuk & Schmidt, 1962) it can be postulated that the pathway for presynaptic inhibition contains at least one serially arranged interneurone, which would, of course, not be antidromically invaded in response to a cortical stimulus; nor would it be expected to be inhibited by a cortical stimulus. On the other hand, it would be expected to respond to an afferent volley by a prolonged repetitive discharge for 10 or more milliseconds in order to account for the prolonged

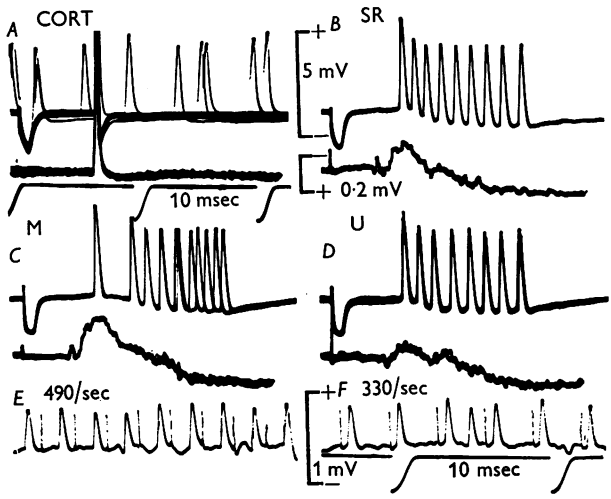

Fig. 15. Responses of a presumed presynaptic inhibitory interneurone. The characteristic high-frequency responses to contralateral nerve volleys are shown in *B–D*, there being two superimposed traces in *C* and *D*, while in the five superimposed traces of *A* the cortical stimulus failed not only to excite the cell but also to inhibit the spontaneous discharge. In *E* the cell followed a stimulation frequency to SR nerve at 490/sec, while in *F* it even gave an interpolated response when following 330/sec. *E* and *F* were taken during a brief repetitive stimulation, the actual stimulus responsible for each spike being many milliseconds earlier than the immediately preceding stimulus artifact.

rising phase of the presynaptic depolarization (Andersen, Brooks, Eccles & Sears, 1964, Figs. 10, 11, 13). Another possible criterion would be absence of synaptic activation by a cortical stimulus, for preliminary tests did not disclose a prolonged presynaptic depolarization to such a stimulus (Andersen, Brooks, Eccles & Sears, 1964, Fig. 12).

Figures 15, 16 show responses of a cell that qualified by all these criteria as a presynaptic inhibitory interneurone. In Fig. 15 *B*, *C*, *D* it responded to all three nerve volleys by a prolonged high-frequency discharge comparable with the discharges observed for assumed presynaptic inhibitory

cells in the spinal cord, yet in *A* its spontaneous discharge was not affected by a cortical stimulus. In Fig. 16*I, J, K* the rhythmic response to an SR volley (delivered alone in *F*) was not affected by a preceding cortical stimulus. However, in Fig. 16*B–E* a preceding SR stimulus depressed the

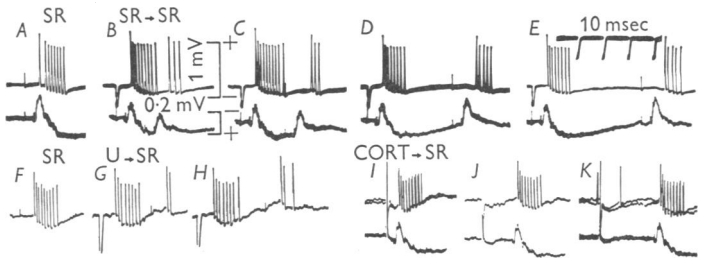

Fig. 16. Conditioning of repetitive spike discharges of a presumed presynaptic inhibitory interneurone. *A* and *F* show the repetitive spike discharges evoked by a contralateral SR volley. In *B–E* this response is seen to be depressed by a preceding SR volley at four different test intervals. In *G, H* there is a similar depression by a preceding U volley. However, in *I–K* a preceding cortical stimulus had no appreciable effect. All responses are at same sweep speed, and voltage scales for thalamic (upper) and cuneate (lower) responses are shown.

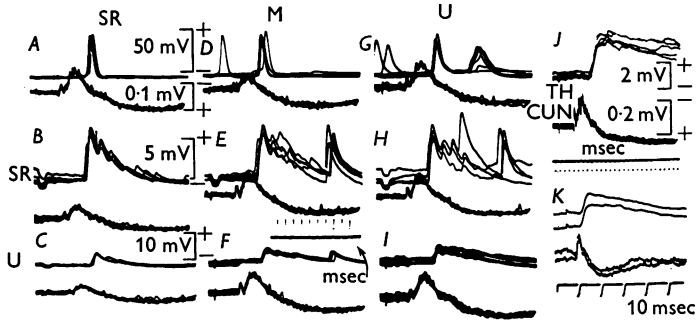

Fig. 17. Intracellular responses from presumed presynaptic inhibitory interneurones. Upper traces are intracellular recordings from thalamic cells, lower traces are from the surface of the cuneate nucleus. *A–I* are responses from one presumed interneurone that gave initially spike responses to SR, M and U contralateral volleys (*A, D, G*). Later, spikes failed as the membrane potential fell. *B, E, H* show EPSPs evoked by a progressively larger SR volley, and similarly *C, F, I* for a U volley. Note separate voltage scales for each row of thalamic responses, but same cuneate scale throughout. *J* and *K* show pure EPSP responses to contralateral afferent volleys by two other presumed presynaptic inhibitory interneurones. Voltage scales for TH and CUN in *J* also obtain for *K*, but there are separate time scales. All records are formed by the superposition of several traces.

response to a second SR, and in *G, H* a conditioning U volley produced a similar depression of an SR response. This inhibition can be sufficiently explained by the presynaptic inhibitory action on the terminals of the

medial lemniscal fibres in the thalamus (Andersen, Brooks, Eccles & Sears, 1964, Figs. 9, 10, 12), which would depress their activation of presynaptic inhibitory cells as well as of thalamo-cortical relay cells. Figure 15*E*, *F* shows that this cell follows high frequency orthodromic stimulation, 490/sec in *E*, while in *F* at 330/sec it even registers one double response. It will be appreciated that in these continued repetitive responses the spikes are not produced by the immediately preceding nerve stimulus.

Figure 17 shows examples of intracellular responses of a thalamic cell that possibly could be a presynaptic inhibitory interneurone, though it usually responded only once to an afferent volley (*A*, *D*, *G*). Later, when the membrane potential had fallen, afferent volleys elicited merely EPSPs of complex composition with later large superimposed EPSPs (*B*, *C*, *E*, *F*, *H*, *I*). Presumably these EPSPs could in part arise from repetitive discharges of cuneate cells and in turn could be the basis of the prolonged repetitive responses often observed (Fig. 15*B–D*). This cell resembled that of Figs. 15, 16 in being neither excited nor inhibited by cortical stimulation, and its identification as a presynaptic inhibitory cell was also indicated by the absence of all trace of an IPSP response. Figure 17*J*, *K* gives examples of potentials evoked by afferent volleys in other thalamic cells, there being prolonged EPSPs with no trace of IPSPs. Possibly these cells are also interneurones on the presynaptic inhibitory pathway.

DISCUSSION

At the outset it is important to recognize that the criteria employed by Poggio & Mountcastle (1963) for defining lemniscal neurones would obtain not only for the thalamo-cortical relay (TCR) cells of Figs. 1–13, but also for the other two cell types that we have attempted to recognize in relation to the postulated interneurones on the post-synaptic (Fig. 14) and presynaptic inhibitory pathways (Figs. 15–17). Each type of interneurone usually gave repetitive responses to single afferent volleys; and Fig. 15*E* shows that a postulated presynaptic inhibitory cell followed a frequency of stimulation of 490/sec. This is a performance superior to the great majority of TCR cells, where no doubt the powerful and prolonged post-synaptic inhibitory action greatly impedes the ability to follow even moderately high frequencies of stimulation. We can conclude that there is no conflict between the exclusive identification of all VBC cells as lemniscal neurones (Poggio & Mountcastle, 1963) and our postulate that the TCR cells represent only a fraction of those VBC cells that are strongly excited by lemniscal volleys.

Lemniscal neurones of the ventro-basal complex have been defined as those neurones that respond to lemniscal volleys by a discharge that has

a short latency and is often repetitive (Poggio & Mountcastle, 1963). Lemniscal neurones that are antidromically activated from the somatosensory cortex have been classified as TCR cells; however, a negative response to this test is indecisive. In part this 'negative' category can be further subdivided into cells synaptically excited from the somatosensory cortex, and those not excited. The former would qualify as interneurones on the postulated post-synaptic inhibitory pathway from axon collaterals of the TCR cells. The latter may be interneurones on the presynaptic inhibitory pathway. However, it must be recognized that some cells failing to respond to the antidromic test may be TCR cells with axonal terminals so remote that the cortical stimulus was ineffective. Two other ancillary criteria are helpful in recognition of cells on the presynaptic inhibitory pathway: on analogy with the spinal cord (Eccles *et al.* 1962) it would be expected that interneurones on the presynaptic inhibitory pathway are excited from a large cutaneous area as in Figs. 15 and 17; and our experiments suggest that such interneurones, being subjected to post-synaptic inhibition (Figs. 16, 17), fire in longer bursts and at higher frequency (Fig. 15) than the TCR cells (Figs. 1*C–E*, 2, 5, 6).

An important finding is illustrated in Figs. 15*A* and 16*I–K*, where cortical stimulation had no inhibitory action on spontaneous or evoked discharges of the presumed presynaptic inhibitory interneurones. Cortical stimulation was also without excitatory action on these interneurones, which may be an important distinguishing feature from the post-synaptic inhibitory interneurones (cf. Fig. 14), though more investigation is required. There should be further investigation here in an attempt to decide whether or not cortical stimulation exerts any appreciable presynaptic inhibition on TCR cells (cf. Andersen, Brooks, Eccles & Sears, 1964, Fig. 12).

There is a further criterion that may be important in distinguishing between TCR cells and interneurones on either of the inhibitory pathways. When recording intracellularly from cells that qualify as TCR on other tests, large and prolonged IPSPs are always produced both by afferent nerve volleys and by cortical stimulation (Figs. 8–13). In contrast, cells that qualified as inhibitory interneurones on other tests have never exhibited signs of post-synaptic inhibition (Figs. 14–17). Provisionally, therefore, even when the full battery of distinguishing tests could not be applied, all lemniscal cells responding by IPSPs have been classified as TCR cells.

The simplest post-synaptic and presynaptic inhibitory pathways are illustrated diagrammatically in Fig. 18*A*, *B*. Figure 18*A* will be discussed in detail later. In accord with the preceding discussion, Fig. 18*B* shows an extensive convergence of collaterals from lemniscal fibres onto a pre-

synaptic I cell, which in turn has synaptic endings on the excitatory synapses of TCR cells in the manner typical for presynaptic inhibition elsewhere (Eccles, 1964).

Of the total of 167 lemniscal neurones in which a provisional classification could be attempted on the basis of the criteria here considered, there were 122 TCR cells, 16 post-synaptic and 29 presynaptic inhibitory relay cells. It will be understood that this is merely an initial tentative classification in accordance with the postulated pathways in the ventro-basal complex and with the modes of excitatory and inhibitory action. In view of

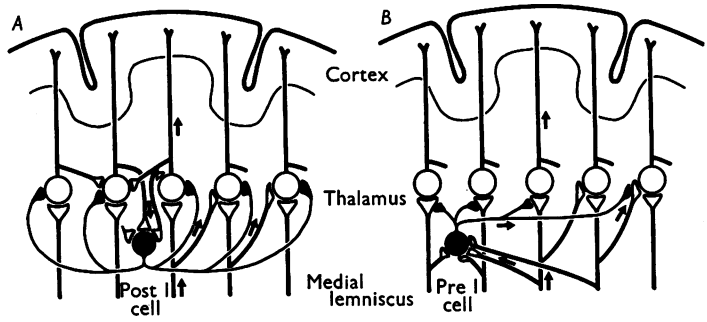

Fig. 18. Diagrams of postulated pathways for post-synaptic (*A*) and presynaptic (*B*) inhibitory actions on transmission through the ventro-basal complex of the thalamus. In *A* the axon collaterals of the TCR cells are seen to excite both TCR cells and the post-synaptic inhibitory interneurone (POST I CELL), which is widely distributed to the excitatory synapses on TCR cells. In *B* branches of medial lemniscal fibres excite the presynaptic inhibitory interneuron (PRE I CELL), which is widely distributed to the synaptic knobs of lemniscal fibres.

the very powerful IPSPs of possibly all TCR cells, the proportion of post-synaptic inhibitory relay cells seems low. However, in the CA1 and CA3 zones of the hippocampus even larger IPSPs are produced in every pyramidal cell by a population of basket cells that is relatively low (Andersen, Eccles & Løyning, 1963, 1964*a*, 1964*b*). Histologically, basket cells are distinguished by the profuseness of their terminal axonal branches (Ramón y Cajal, 1911; Lorente de Nó, 1934) so that one basket cell achieves synaptic contact with between 200 and 500 pyramidal cells. An alternative explanation of the apparent sparseness of post-synaptic inhibitory cells in the VBC may be that they are concentrated in more peripheral zones of the VBC or even just beyond its confines, and so have eluded our micro-electrode explorations, which were not systematically applied to the whole VBC, but merely restricted to areas with a high density of lemniscal cells and large field potentials.

Many weeks after excision of the somato-sensory cortex there is a wide-

spread degeneration of the thalamic cells projecting to this cortex (Walker, 1938; Sheps, 1945; Combs, 1949, 1951; McLardy, 1950; Powell, 1952; le Gros Clark & Powell, 1953) and even an almost total degeneration of the VBC cells has been reported (le Gros Clark, 1936). However, most investigators have found that a considerable proportion of these cells survive (see le Gros Clark & Powell, 1953), which could correlate with the present provisional classification, according to which more than one quarter of the VBC cells would be interneurones and hence not directly affected by cortical ablation. It may further be noted that, if the post-synaptic inhibitory relay cells depended wholly or in large part, for their activation, on axon collaterals of thalamo-cortical relay (TCR) cells, they might also suffer transneuronal degeneration when the TCR cells degenerated, as has been suggested by Amassian (1952). Another possibility is that some TCR cells survive cortical ablation because they have such a wealthy plexus of axon collaterals in the thalamus. Evidently it is important to have further histological investigation at various stages of the degeneration following one or other of these operative procedures: cortical ablation, and cutting of the medial lemniscus.

Before attempting to give an account of the way in which rhythmic burst responses of TCR cells are generated, it is necessary to review the evidence for the postulates that axon collaterals of TCR cells have both an excitatory and an inhibitory action on TCR cells, this latter action of course being mediated by interneurones. Figure 4 illustrates a common finding that cortical stimulation may evoke a second or even a third discharge after the initial antidromic invasion of a TCR cell, and this second discharge may arise from a prepotential resembling a synaptically induced depolarization. In Fig. 2*A* signs of several spike potentials are also seen superimposed on the slow negative wave that followed the initial antidromic spike potential, and this slow negative wave is also evident in Fig. 8*A*. Synaptic excitatory action by axon collaterals is further indicated in Fig. 7*G–J*, where, at an early stage of recovery from the P-wave, cortical stimulation evoked a repetitive spike response.

The production of IPSPs by cortical stimulation is well illustrated in Figs. 9, 11 and 13*G–J*. The latency may be as brief as 2·0 msec (Andersen & Eccles, 1962, Fig. 1*F*), which allows time for the interposition of one interneurone. The pathway would involve, in sequence, antidromic propagation from the cortex in the axons of TCR cells, then propagation through axon collaterals to the inhibitory interneurones which are activated as illustrated in Fig. 15. These in turn would generate IPSPs of the TCR cells, as shown diagrammatically in Fig. 18*A*.

Intracellular recording from TCR cells (Figs. 8, 9, 11, 13) clearly establishes that the IPSP plays a dominant role in suppressing impulse discharge

in the periods between the successive burst discharges. When TCR cells are activated either by a lemniscal volley (Figs. 8*B*, 9*A–C*) or by cortical stimulation (Figs. 9*D–I*, 13*I*, *J*), the abrupt onset of the IPSP cuts off all further TCR cell discharges, and this can also be observed with extracellular recording (Figs. 2*F–I*, 6). The same abrupt suppression of impulse discharge by the IPSP can be recognized after the first burst discharge in Figs. 9 *B*, *C*, *F*, *G* and 13*I*, *J*; but it is not so clearly defined in Fig. 2*F–I*, where the spike discharges became more out of phase with successive bursts. For the present it is sufficient to note that the initial IPSP is satisfactorily accounted for by the postulate that it is produced by impulses discharged by TCR cells operating through their axon collaterals on to inhibitory neurones, and so back to TCR cells as in Fig. 18*A*. The repetitive discharge of inhibitory interneurones (see Fig. 14) accounts for the long rising phase of the IPSP. In addition it must be postulated that axon collaterals from many TCR cells converge on an individual inhibitory interneurone, which, reciprocally, is widely distributed in its inhibitory action on TCR cells. It is of interest that Ramón y Cajal (1911, Fig. 263) illustrated thalamic cells with a considerable branching of their axon collaterals.

Additional postulates are required in order to account for the generation of the first burst discharge. First, it is postulated that late on the declining phase of the IPSP the TCR cells are in the hyperexcitable phase of post-anodal exaltation or 'rebound'. This effect has been demonstrated after anodal polarization of spinal ganglion cells (Ito, 1957) or motoneurones (Coombs, Curtis & Eccles, 1959; Araki, Ito & Oshima, 1961), and after IPSPs both of motoneurones (Coombs, Eccles & Fatt, 1955) and of pyramidal cells of the hippocampus (Kandel & Spencer, 1961). An additional explanation may be that a background of synaptic excitation brings the cell to discharge as the IPSP declines. This background excitation could be exercised by interneurones whose discharges could themselves conceivably be phased by the rhythmic inhibitory process.

Those cells with the largest IPSPs would be the most likely to generate a discharge late on the declining phase; and, because of the synchrony in the generation of the IPSPs, all TCR cells recovering from large IPSPs would be in a hyperexcitable state at this time. Thus, the first rhythmic burst discharge in Figs. 9 and 13*I*, *J* may be sufficiently explained as the reaction to post-anodal exaltation, with local responses growing up to full size impulses, during the terminal stages of the IPSP. Direct excitability testing has disclosed a phase of hyperexcitability of TCR cells that is exactly synchronized with the burst discharge (Andersen, Brooks, Eccles & Sears, 1964, Figs. 10, 11, 12). In addition to this spontaneous development of post-anodal exaltation in the population of TCR cells, some sort of

interaction between these cells is indicated by the synchronization of the burst discharges of a population of TCR cells (Andersen, Brooks, Eccles & Sears, 1964, Figs. 2, 5). In part this could be due to ephaptic interaction, the impulses generated by the earliest discharging TCR cells triggering by electrical current flow the discharges in neighbouring hyperexcitable cells. However, the excitation of TCR cells by axon collaterals of other TCR cells (Figs. 4, 18*A*) must play a significant role in this synchronization. This is particularly important in accounting for the discharge of repetitive bursts and for the initiation of such discharges by a single antidromic volley from the cortex (Fig. 7*G–J*).

The first burst discharge would again excite the inhibitory neurones through the axon collaterals, and so again terminate itself by the IPSPs it generated, from which recovery would again recur in a phase of exaltation and generation of the second burst discharge, and so on. Provided that the post-synaptic inhibition generated by each burst discharge is distributed sufficiently widely to the thalamic neurones, there appears to be no need to postulate any phasing device other than the rhythmically generated IPSPs. Purpura & Cohen (1962) have proposed similarly that rhythmically generated IPSPs are responsible for the phasing of the burst discharges, but they did not envisage that the IPSP production could be due to a recurrent inhibitory pathway through axon collaterals of TCR cells.

Figure 18*A* explains how the antidromic impulses evoked by stimulation in the sensory cortex of the axonal terminals of thalamic neurones would also activate the inhibitory neurones through the axon collaterals; hence this stimulation should be just as effective as orthodromic activation in evoking the rhythmic inhibitory post-synaptic potentials and the rhythmic burst discharges from the thalamus. This is indeed observed with the somato-sensory cortex (Figs. 2, 8, 9, 11, 13), and analogously Bishop & Davis (1960) found that stimulation of the optic radiation evoked rhythmic discharges of lateral geniculate neurones. Furthermore, the pathways of Fig. 18*A* offer a satisfactory explanation of the way in which intercurrent orthodromic (Andersen, Brooks, Eccles & Sears, 1964, Fig. 5*A–G*) or antidromic (Fig. 9*J–L*, *N–P*) stimulation affected the rhythmic burst discharge.

It will be evident that the hypothesis here formulated belongs to the category in which the duration of the rhythmic cycle is determined by the intrinsic properties of the neurone, as has been proposed by Bremer (1949, 1953) and by Clare & Bishop (1956), and is not set by the transmission time through a complex neuronal pathway. However, the hypothesis is unique in that it has not previously been postulated that the essential phasing device is due to widely dispersed inhibitory post-synaptic potentials that are generated through a recurrent pathway from axon collaterals.

It remains to suggest that the very large and prolonged recurrent inhibitory post-synaptic potentials of neo-cortical and hippocampal pyramidal cells (Phillips, 1959, 1961; Albe-Fessard, 1960; Kandel, Spencer & Brinley, 1961; Lux & Klee, 1962; Li & Chou, 1962; Andersen, Eccles & Løyning, 1963, 1964*a*, *b*) may also be similarly concerned as the phasing device for the basic alpha and theta rhythm, respectively, the IPSPs contributing very largely to the potential waves of these rhythms.

SUMMARY

1. By means of various experimental criteria it has been possible to classify into three groups the cells of the ventro-basal complex of the thalamus that are activated from the medial lemniscus (the so-called lemniscal cells). Of a total of 167 lemniscal cells, the great majority (122) were classified as thalamo-cortical relay (TCR) cells, the remainder being presumed to be interneurones on inhibitory pathways, 16 post-synaptic and 29 presynaptic inhibitory interneurones.

2. The two essential criteria for identifying TCR cells are synaptic activation from a contralateral afferent nerve and antidromic invasion from the ipsilateral somato-sensory cortex. The accumulated evidence also indicates that, in contradistinction to the inhibitory interneurones, all TCR cells are post-synaptically inhibited both by contralateral afferent volleys and by stimulation of the ipsilateral somato-sensory cortex. This post-synaptic inhibition is revealed both by a prolonged suppression of spontaneous discharge and by inhibition of the response evoked by another testing afferent volley.

3. Intracellular recording from TCR cells reveals large and prolonged IPSPs, which, typically, are inverted by an increase in intracellular chloride concentration. These IPSPs are produced by subcortical stimulation after degeneration of all cortico-thalamic fibres. In addition, their short latency conforms with the postulate that they are generated by a typical recurrent inhibitory pathway, axon collaterals of TCR cells to post-synaptic inhibitory interneurones and so to inhibitory synapses on TCR cells. In accord with this postulate the latency of the monosynaptic EPSPs produced by lemniscal volleys is found to be at least 1·5–2 msec shorter than the earliest IPSPs.

4. Intracellular recording from TCR cells demonstrates the dominant role of the IPSPs in generating and in phasing the rhythmic potential waves with superimposed burst discharges that are such a characteristic feature of thalamic responses to orthodromic or antidromic stimulation.

5. By definition neither type of interneurone is antidromically invaded in response to cortical stimuli. In accord with the above postulate of

recurrent inhibition, those interneurones synaptically activated in response to cortical stimuli are regarded as being post-synaptic inhibitory interneurones. Besides this negative criterion for their identification, presynaptic inhibitory interneurones also give prolonged high-frequency discharges in response to a wide variety of afferent volleys, and these discharges are not affected when post-synaptic inhibitory action suppresses TCR discharges.

6. An hypothesis is developed that accounts for all the findings as to rhythmic thalamic responses to orthodromic and antidromic activation. Essentially the phasing of the rhythm is attributed to a widespread recurrent IPSP that is produced by the discharges of TCR cells, while the subsequent burst discharge is attributed to the post-anodal exaltation or rebound that occurs on recovery from the prolonged large IPSPs. The demonstrated positive feedback by excitatory axon collaterals will account for the rapid spread of this excitation through the population of TCR neurones, but ephaptic spread may also contribute to the first burst discharge. This burst discharge of course immediately results in a second recurrent IPSP of the TCR population, which again recovers to the second burst discharge, and so on.

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