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THE VENTRO-BASAL NUCLEUS OF THE THALAMUS: POTENTIAL FIELDS, SYNAPTIC TRANSMISSION AND EXCITABILITY OF BOTH PRESYNAPTIC AND POST-SYNAPTIC COMPONENTS

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In 1941 Marshall recorded spike potentials and slow potential waves from the thalamus of the cat. In response to a single volley in a cutaneous nerve there was a brief high-frequency discharge of thalamic cells followed by a prolonged positive potential with an associated depression of synaptic transmission for as long as 150 msec. Transmission in the somato-sensory pathway through the thalamus has since been the subject of several investigations (Mountcastle & Henneman, 1949, 1952; Amassian, 1952; Hunt & O'Leary, 1952; Mountcastle, Covian & Harrison, 1952; Rose & Mountcastle, 1952, 1954, 1960; Gaze & Gordon, 1954; Kruger & Albe-Fessard, 1960). In these studies attention was largely concentrated on the spike discharges and on the topographical representation in the thalamic nuclei, but the prolonged depression in the somato-sensory pathway following a conditioning afferent volley was observed by Mountcastle *et al.* (1952), Amassian (1952), Mountcastle & Powell (1959) and Mountcastle, Davies & Berman (1957). Poggio & Mountcastle (1963) used the number of impulses discharged by thalamic cells as a measure of the depression produced by a conditioning afferent volley, and found that the duration of the depression was in excess of 100 msec in an anaesthetized animal, and 70 msec when the animal was unanaesthetized.

In 1941 Adrian observed that a single afferent volley evoked a rhythmic thalamo-cortical discharge, which occurred in short bursts repeated at a frequency of 10–20/sec, and which was shown to be generated in the thalamus because it still occurred when the somato-sensory cortex was inacti-

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vated or ablated. These rhythmic burst discharges that an afferent volley evokes from the thalamus have also been observed by Jarcho (1949), Chang (1950), Bremer & Bonnet (1950), Gaze & Gordon (1954), and Purpura & Cohen (1962); and further experimental observations on them will be reported in this, and in the following paper (Andersen, Eccles & Sears, 1964).

In general the thalamic investigations here briefly reviewed indicate that the somato-sensory pathway through the thalamus involves a fairly complex neural mechanism. In the present paper this mechanism has been studied by three types of experiments on the ventro-basal complex of the thalamus: by extracellular recording of field and spike potentials in the thalamus; by the conditioning of discharges from thalamic cells to the cortex either by an afferent volley or by a single cortical stimulus; and by testing the excitability changes of the post-synaptic and presynaptic components. This excitability testing was effected by brief electrical pulses applied near to the synapses in the thalamus through a microelectrode; and two kinds of evoked responses were recorded, namely, the impulses transmitted to the somatosensory cortex, and the medial lemniscal volley generated in the presynaptic terminals in the thalamus and antidromically transmitted to the cuneate nucleus. This experimental procedure provides three tests of excitability: direct excitability of thalamocortical relay cells; excitability of thalamo-cortical relay cells secondary to the excitation of presynaptic terminals; direct excitability of presynaptic terminals, which provides a test for the depolarization that is responsible for presynaptic inhibition. All these tests have been applied in investigating the conditioning of thalamic synapses either by previous afferent volleys in cutaneous nerves or by stimulation of the somato-sensory cortex or of the underlying white matter. It will appear that thalamic transmission is subject to a powerful and long-lasting post-synaptic inhibition, and that often, in addition, there is a presynaptic inhibition.

METHODS

Adult cats were used, anaesthetized with pentobarbital sodium, 40 mg/kg body weight. Additional doses were given when necessary to keep the animals at a moderate level of anaesthesia. After removal of the skull, the middle portions of the lateral, suprasylvian and ectosylvian gyri were removed by suction. The rostral border of the cortical ablation was restricted so that all the thalamo-cortical fibres to the somato-sensory areas I and II were left intact. After exposure of the lateral ventricle, the fimbria and the hippocampus were removed with a glass seeker, thus exposing the dorsal surface of the thalamus in the telo-diencephalic fissure.

The recording electrodes were introduced through small holes in the pia on the dorsal surface of the thalamus. The ventro-basal complex of the thalamus (VBC) was reached when the electrode was inserted between 5 and 9 mm from the mid line, and from 6 to 9 mm

below the dorsal surface of the thalamus. The rostral and caudal borders were found in a sagittal plane, 6 mm from the mid line and approximately 2 mm in front of and 2 mm behind the fissure that separates the thalamus from the striatum. The borders of the ventro-basal complex were outlined by inserting the electrode in a series of tracks arranged in a rectilinear grid with 1 mm inter-track distance. In six animals the electrodes were moved up and down several times in a track that gave typical potential fields and the track was subsequently identified histologically in serial sections stained with thionin according to the method of Spielmeyer. Micro-electrode insertion was sometimes performed with the use of ordinary Horsley–Clarke co-ordinates. The two methods showed good correlation. The exposure of the dorsal thalamus allowed a more precise location of the electrodes than otherwise would have been possible, and reduced the capacitive effect of the surrounding tissue on the recording electrodes by reducing the immersed length of the electrodes.

The left somato-sensory cortex was exposed, and the whole of the brain covered with paraffin oil at 37° C in a pool made from the skin flaps. The paraffin was kept warm by a small heating lamp. In the later experiments the brain tissue was irrigated with Ringer–Locke fluid at 37° C, and subsequently the thalamus was covered with 4 % agar in Ringer–Locke solution as previously described (Andersen, Eccles & Løyning, 1964).

The right superficial radial (SR), median (M) and ulnar (U) nerves were dissected and mounted on bipolar stimulating electrodes in a small pool made by the skin flaps of the foreleg. Usually the dorsal column nuclei were also exposed in order to monitor the afferent volley passing through these structures towards the thalamus. Antidromic stimulation of the thalamo-cortical axons was effected by means of bipolar stimulating electrodes with a separation of 2 mm on the arm area of the somato-sensory cortical area I.

The recording electrodes were glass micro-pipettes, filled with solutions of either 4 M-NaCl, 3 M-KCl, or 2 M-K-citrate, and with a resistance of 7–25 MΩ. The signals obtained from the micro-electrodes were fed through a cathode follower and displayed on the oscilloscope through an a.c.-coupled amplifier or alternatively through a d.c.-coupled amplifier which also was connected to a voltmeter that recorded the membrane potential. Surface records from the somato-sensory cortex and from the cuneate nucleus were made with thin platinum-wire electrodes ending in a small ball. Recordings from the killed ends of the thalamo-cortical fibres were made from the white matter underlying the cortex by using a 0·5 mm thick platinum wire insulated with polyethylene. The end of this electrode was cut off squarely. After the cortex had been sucked away the electrode was moved over the surface of the white matter in order to find the optimal recording point. Even larger signals were obtained by pushing the electrode approximately 1 mm into the white matter.

Testing for the excitability of the presynaptic terminals of the medial lemniscal fibres in the ventro-basal complex was performed by using relatively coarse glass micro-electrodes filled with 4 M-NaCl and with a resistance from 0·5 to 1·5 MΩ. The test stimulus was a pulse applied between this micro-electrode and earth, and the resulting antidromic potential was recorded by means of an electrode resting on the surface of the cuneate nucleus. A conditioning volley was applied to either of the foreleg nerves or to the somato-sensory cortex at various times preceding the test stimulus to the ventro-basal complex. Testing for post-synaptic excitability was performed simultaneously with the use of the same electrode and stimulating technique, but with recording by the 'killed end' technique from the white matter of the cortex.

In thirteen animals, the somato-sensory cortex was removed under aseptic conditions, 5–22 days before the acute experiment. In ten animals, only the somato-sensory area I was removed on the same side as the thalamus to be studied, and, in the remaining three animals, both the areas I and II of the somato-sensory cortex were removed.

RESULTS

Field potentials in the ventro-basal nucleus

Generated by nerve volleys. As described in Methods, the standard procedure has been to insert the micro-electrode from the dorsal surface of the thalamus, exposed after removal of the parietal cortex and the hippocampus by suction. While the micro-electrode was being slowly advanced, each nerve, superficial radial (SR), median (M) and ulnar (U), was electrically stimulated in quick succession so that the passage of the micro-electrode into and through the ventro-basal nucleus was graphically shown by the evoked potentials. Sometimes several exploratory insertions were required before the large size of the evoked potentials showed that the micro-electrode was recording focally from a region where there was a high density of synaptic endings of the medial lemniscus fibres from the cuneate nucleus.

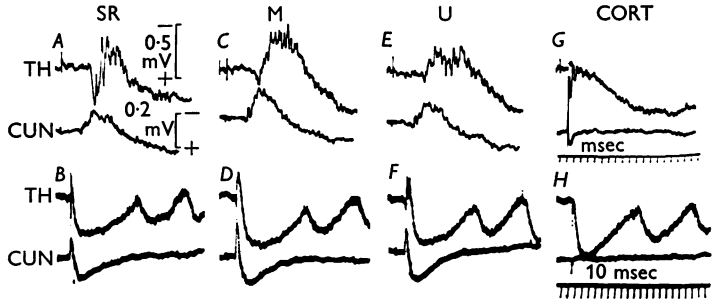

Fig. 1. Simultaneous thalamic and cuneate potentials. Upper traces (TH) are potentials recorded by a micro-electrode in the ventro-basal complex of the thalamus with respect to an indifferent earth lead; lower traces (CUN) are also unipolar, being simultaneously recorded from the dorsal surface of the contralateral cuneate nucleus. In *A*, *C*, *E* the stimulus artifact at the beginning of each trace gives the time of stimulation of the contralateral superficial radial (SR), median (M) and ulnar (U) nerves at about 4 times threshold strength. *G* gives potentials similarly recorded but in response to a single stimulus applied to the ipsilateral somato-sensory cortex through bipolar electrodes, as described in Methods. *B*, *D*, *F* and *H* correspond to the respective upper traces but are recorded at the much slower sweep speed as shown. The potential scales in *A* are for all thalamic and cuneate responses, respectively.

Usually, as in Fig. 1*C*, *E*, the thalamic potential evoked by a single afferent volley began with a brief diphasic (positive-negative) spike that is presumably due to the arrival of the earliest discharges in the lemniscal fibres, and is equivalent to the presynaptic complex of Rose & Mountcastle (1954). It was only 1·5–2 msec later than the presynaptic spike potential in the cuneate nucleus (lower traces of Fig. 1*C*, *E*). In Fig. 1*A* the large

initial positive spike is attributable to injury of some of the terminal branches of lemniscal fibres excited by the SR volley. In Fig. 1*A*, *C*, *E*, the subsequent negative potential with superimposed spikes will be referred to as the N-wave, because, just as in the cuneate nucleus, it is largely produced by synaptic excitation of the thalamic neurones. In less than 10 msec the N-waves are seen to pass over to positive potentials (P-waves) which in the corresponding slower traces (Fig. 1*B*, *D*, *F*) have a duration of about 100 msec.

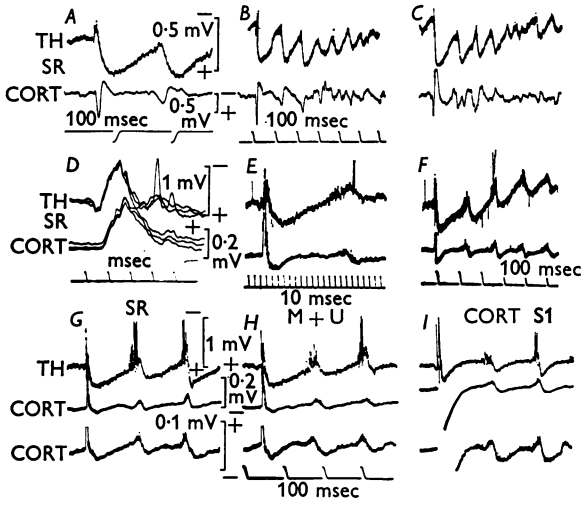

Fig. 2. Simultaneous thalamic and cortical potentials. In *A*, *B*, *C* a single stimulus to the contralateral SR nerve evoked thalamic potentials recorded as in Fig. 1B (upper traces) and potentials unipolarly recorded from the surface of the arm area of somato-sensory cortex (lower traces). Note potential scales for these two traces, and also that *B* and *C* were recorded at a much slower sweep speed, as indicated. *D*, *E*, *F* were also evoked by an SR volley, but in another experiment in which the CORT recording was from the white matter exposed after sucking away the somato-sensory cortex, *D* being produced by three superimposed traces. Note large changes in the sweep speed, but the potential scales for the TH and CORT records in *D* apply also to *E* and *F*, the CORT recording being inverted as shown. The CORT recordings in *G*, *H*, *I* were also from the exposed white matter, and are shown at two amplifications. The responses were evoked by contralateral SR and M + U nerves and also (CORT S1) by an ipsilateral stimulus to the white matter of somato-sensory area I.

The P-waves in Fig. 1*B*, *D*, *F* terminate in peaks of relative negativity on which there are usually superimposed repetitive spike discharges, called the first burst discharge, and then another P-wave supervenes with a time course always briefer than the first, and this in turn leads to a new, relatively negative, wave and a further P-wave. In the upper traces of

similarly recorded responses in Fig. 2*B* and *C* there are sequences of eight P-waves of progressively diminishing size, and in Fig. 2*F* there are five. In these records the first P-wave is from 100 to 140 msec in duration, whereas subsequent P-waves are at least 20% briefer. Repetitive spike discharges can be seen superimposed on the negative waves between each successive P-wave, as in Fig. 2*E–H*, and these will be designated burst discharges. Apparently these give the rhythmic thalamo-cortical responses described by Adrian (1941, 1951), Jarcho (1949), Chang (1950) and Gaze & Gordon (1954).

Simultaneous recording from the thalamus and somato-sensory cortex as in Fig. 2*A* shows that the thalamic N-wave is closely followed by an evoked cortical potential with its typical positive-negative configuration, as first described by Adrian (1941), Marshall, Woolsey & Bard (1941) and Marshall (1941); and the first burst discharge also evoked in the cortex a similar wave, but of lower amplitude and longer duration, which suggests a more asynchronous thalamic discharge. In the slower record of Fig. 2*B* there is also a recognizable correspondence of thalamic and cortical responses throughout the whole series of the thalamic burst discharges, but there was an intercurrent disturbance by spontaneous cortical activity. In Fig. 2*C* there was even more disturbance by a background of cortical activity; but at least the initial evoked response and the response evoked by the first burst discharge are recognizable in the cortical trace. When the grey matter of the somato-sensory cortex was removed by suction, the evoked response was a pure positive potential owing to 'killed-end' recording from the thalamo-cortical fibres, as is well seen in the fast records of Fig. 2*D* (lower trace). Under such conditions there is excellent correspondence between each burst discharge in the thalamus and the positive wave in the lead from the white matter left after removal of the somato-sensory cortex (Fig. 2*E*, *F*, *G*, *H*). Evidently, in agreement with Adrian (1941, 1951), the repetitive burst discharges in the cortex must be attributed to discharges from the thalamus. The records from the cuneate nucleus in Fig. 1 showed that the nerve volleys evoked the typical N- and P-waves (Therman, 1941; Andersen, Eccles, Schmidt & Yokota, 1964*a*), but there was never any trace of activity resembling the burst discharges (Fig. 1*B*, *D*, *F*), which must be generated further cephalad.

Two opposing explanations have been offered for the mode of production of the rhythmic burst discharges. Chang (1950) stated that this rhythmic response was never observed after cortical ablation, and hence postulated that the rhythm was generated by a thalamo-cortical reverberatory circuit. Adrian (1941, 1951), on the contrary, observed that the rhythmic thalamic discharge persisted after inactivation or removal of the cortex, and hence postulated that it was an intrinsic thalamic response. The

present investigation unequivocally supports Adrian's work. Figure 3*A–C* shows rhythmic responses of the thalamus generated by volleys in SR, U and M nerves, respectively. After removal of the somato-sensory cortex (Fig. 3*D–F*), there was no detectable change in the rhythmic responses. After a further very extensive ablation with removal of all parts of the cortex connected to the ventro-basal nucleus, the nerve volleys still evoked the rhythmic waves (Fig. 3*G–I*). Rhythmic burst discharges have been observed as long as 12 days after excision of the somato-sensory cortex (Andersen, Eccles & Sears, 1964, Fig. 13), at which time many

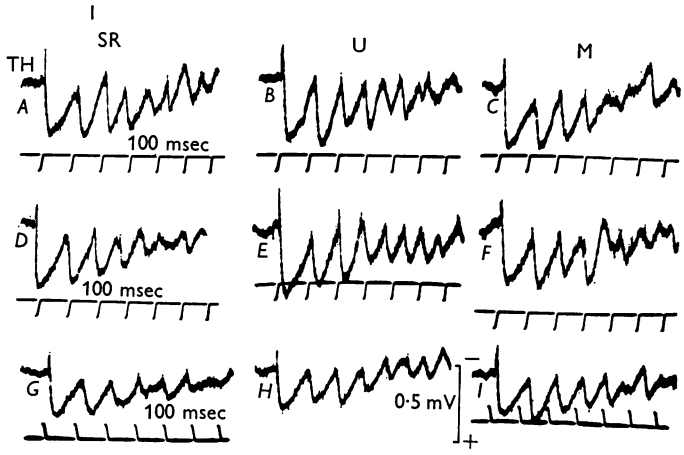

Fig. 3. Effect of cortical ablation on rhythmic thalamic waves. *A*, *B*, *C* are thalamic potentials recorded as in Fig. 1 and evoked by single contralateral SR, U and M volleys as indicated. *D*, *E*, *F* are similarly recorded after ablation of the ipsilateral post-cruciate cortex and in *G*, *H*, *I* there had been a much wider cortical ablation. All recordings were from the same site in the thalamus and at the same amplification and sweep speed.

thalamo-cortical relay cells have not undergone chromatolytic degeneration. The persistence of a rhythmic thalamic response after cortical ablation does not of course exclude the possibility of an additional intracortical mechanism for a similar rhythm.

Generated by cortical stimulation. A single brief electrical stimulus applied to the somato-sensory cortex or to the white matter in a chronically decorticate preparation initiates within 0·2 msec a diphasic (positive-negative) spike potential in the thalamus (Fig. 1*G*), produced by the volley propagating antidromically in the thalamo-cortical fibres. Often this diphasic spike is followed by one or more smaller spikes (Fig. 1*G*), and these will be further considered in the next paper (Andersen, Eccles & Sears, 1964). Our present interest is in the large P-wave that follows

(Fig. 1*G*), and which in Fig. 1*H* is seen to be the first phase of a rhythmic series of waves with burst discharges exactly comparable with those evoked by nerve volleys. Figure 2*I* shows that these burst discharges are associated with the discharge of impulses to the cortex, just as are the burst discharges evoked by nerve volleys (Fig. 2*G*, *H*). Likewise the burst discharges evoked by cortical stimulation are quite independent of the cortical grey matter, both the stimulating and recording electrodes in Fig. 2 being applied to the white matter under the somato-sensory cortex after removal of a very extensive area of grey matter by suction.

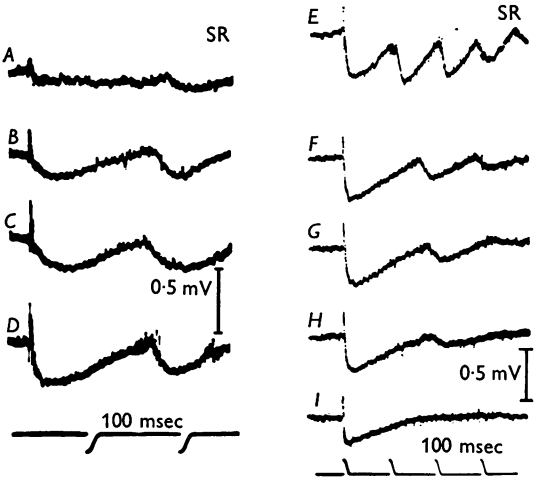

Fig. 4. *A–D* show effect of progressively increasing stimulation up to maximal (*D*) of the contralateral SR nerve on the thalamic potentials recorded as in Fig. 1. *E* shows thalamic rhythmic waves similarly evoked by an SR volley and *F–I* show the effect of progressive deepening of anaesthesia at approximately equal intervals during the first 2 min after an intravenous injection of Nembutal 15 mg/kg.

Further experiments on the field potentials. In Fig. 1*B*, *D*, *F*, *H* all four inputs are seen to produce burst discharges of similar periodicity, and this is also seen in Figs. 2*G–I* and 3. Even a very large diminution in the size of the nerve volley makes no significant change in the duration of the first cycle in Fig. 4*A–D*. However, as reported by Adrian (1941) and Chang (1950), an increase in the depth of anaesthesia slowed the rhythm and decreased the sizes of the burst discharges (Fig. 4*F–H*), leaving eventually (*I*) only the first P-wave.

The effect of an intercurrent nerve volley on the burst discharge is shown in Fig. 5*A–G*, where *A* is the response to the SR volley alone, and at the various times shown by the arrows there is interposed an M volley

(control in *G*). Comparison of *F* with *A* shows that little change was produced by the earliest interposition, but in *E* the first burst discharge was delayed, and the second even further delayed. In *D* the first burst discharge appears to be split into two, as if the first part was a diminished response to the SR volley and the second part was a supplementary response to the M volley, though in that case it would be rather earlier after the M volley than in the control (*G*). In *C* the M volley itself evoked a large N-wave with superimposed spikes, and the first burst discharge occurred at an interval intermediate between the control positions for

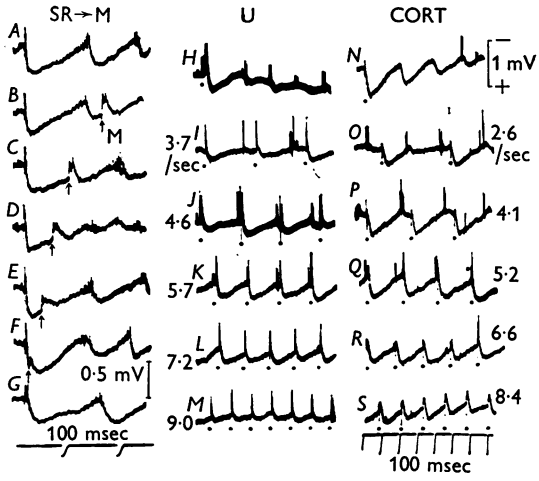

Fig. 5. Effect of repetitive stimulation on thalamic potentials. In series *A–G* the thalamic potentials evoked by single contralateral SR and M volleys are shown in *A* and *G*, respectively, while in *B–F* the M volley was set up at various times (see arrows) after the SR volley. Further description in text. *H–M* show thalamic potentials evoked by a single contralateral U volley (*H*) and by repetitive U stimulation (*I–M*) at the indicated frequencies, the stimuli being indicated by dots. Similarly *N* is the response evoked by a single ipsilateral cortical stimulus and in *O–S* there was repetitive stimulation at the indicated frequencies. It should be noted that all the repetitive series were recorded during a brief tetanus, the onsets not being shown. Same time and potential scale for records *H–S*.

the SR and M volleys alone, too late for the former and too early for the latter. Finally, when the M volley followed the first burst discharge (*B*), it caused a delay in the second burst discharge. It must be recognized that at intervals up to 100 msec after the SR volley the action of the M volley in Fig. 5*A–G* was probably much depressed because of inhibition in the cuneate nucleus (see Andersen, Eccles, Oshima & Schmidt, 1964).

Figure 5*H–M* illustrates another means of investigating the effect of repetitive stimulation on the burst discharges which are evoked in the

control record (*H*) by a single U volley. *I* to *M* were photographed during brief tetani of the U nerve at the indicated frequencies. At 3·7/sec each successive nerve volley was out of phase with the burst discharges, being much later than the first burst discharge after the preceding volley. At 4·6/sec the discrepancy was smaller, and an in-phase relation was almost attained at 5·7/sec, where each stimulus was in the latter part of the burst discharge or just followed it. The stimulus intervals of about 180 msec were then in reasonable accord with the intervals between the burst discharges in Fig. 5*H*, 230 msec for the first burst and about 140 msec between the subsequent bursts. At the still higher stimulus frequencies of 7·2 and 9·0/sec, each stimulus anticipated the burst discharge to the preceding stimulus, so the thalamic discharges were driven strictly in phase with the rhythmic stimuli.

Repetitive stimulation of the somato-sensory cortex in Fig. 5*N–S* allows the phased relation of the stimulation to the burst discharges to be investigated without the complication of the cuneate inhibition that occurs with repetitive nerve stimulation. In Fig. 5*Q* at 5·2/sec each cortical stimulus was almost in phase with the burst discharge to the preceding stimulus. The stimulus intervals of about 190 msec were then very little longer than the burst discharge cycles in Fig. 5*N*, which were successively 190, 180 and 165 msec. As in Fig. 5*L* and *M*, with stimulation frequencies of 6·6 and 8·4/sec (*R*, *S*), each stimulus anticipated the burst discharge, and as a consequence the P-waves were reduced and all burst discharges were suppressed. However, in contrast to the repetitive nerve stimulation (Fig. 5*L*, *M*), each cortical stimulus at these frequencies directly evoked little or no discharge of impulses in the thalamus, which corresponds to the observations with single cortical stimuli (Fig. 1*G*).

When the recording micro-electrode was moved away from the optimal depth for P-wave recording, there was merely a decline in the size of the P-wave, never a reversal. However, it must be recognized that the direction of the micro-electrode track was approximately at right angles to the transmission line through the ventro-basal nucleus from medial lemniscus to the thalamo-cortical radiation. Sinks for the P-wave sources would presumably have been observed if the line of insertion had been oriented along the line of transmission.

Figures 1–5 were chosen for illustration because of the well developed character of the rhythmic responses of the thalamus. In many experiments the P-waves are poorly developed and less regular. In part this deficiency is due to an unfavourable location of the micro-electrode track, but the level of anaesthesia is also important, and, in our experience, rhythmic burst discharges tend to be best at a moderate depth of the barbiturate anaesthesia.

Transmission of impulses through the thalamus

When the cortical grey matter of the somato-sensory area is removed by suction, discharges along the thalamo-cortical fibres give positively directed spike potentials when the recording electrode is placed upon the killed ends of these fibres, as may be seen in the fast record of Fig. 2 *D*. Though there is considerable asynchronism between the impulses evoked by a forelimb afferent volley, their monophasic character allows integration so that the height of the recorded positive wave gives an approximate

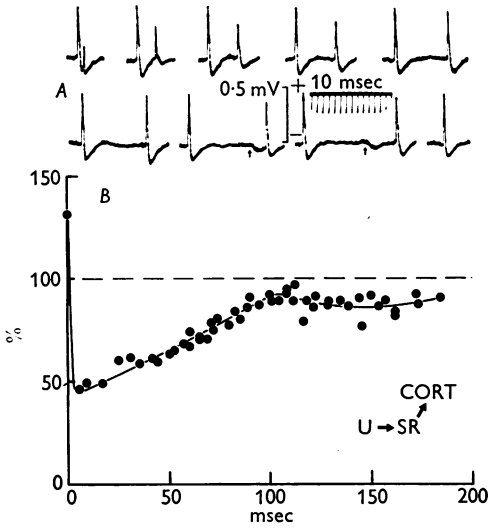

Fig. 6. Conditioning of somato-sensory pathway. *A*. Specimen records of mass discharges evoked by afferent nerve volleys in the contralateral thalamo-cortical fibres, the recording being from the killed ends of these fibres after sucking away the somato-sensory cortex (cf. lower traces of Fig. 2 *D*). The last record of the second row is the response to SR volley alone, and in all others the SR response was conditioned by a preceding U volley over a wide range of testing intervals. The arrows signal the first burst discharges to the U volley. In *B* the sizes of the SR potentials as percentages of the mean control are plotted against the corresponding U–SR testing intervals.

measure of the size of the thalamo-cortical discharge. In the specimen records of Fig. 6 *A* the positive wave produced in this way by an SR afferent volley was used to test for the inhibitory action of a conditioning U volley. Plotting in Fig. 6 *B* of the sizes of the test responses shows that the depression was greatest within 10 msec after the conditioning volley and recovery was almost complete just beyond 100 msec, but thereafter there appeared to be a slight further increase in depression. It will be

appreciated that much of the inhibitory action revealed in Fig. 6 will occur in the synaptic relay in the cuneate nucleus (Marshall, 1941; Gordon & Paine, 1960; Andersen, Eccles, Oshima & Schmidt, 1964). However, the transient phase of relative recovery at about 100 msec has not been observed when testing for cuneate transmission alone. As would be expected, it will later be shown that the inhibitory action at the thalamic relay may be terminated by the transient excitation that is associated with the first burst discharge, which actually was observed at just this location in the thalamic records and also in the cortical records at the arrows in Fig. 6*A*.

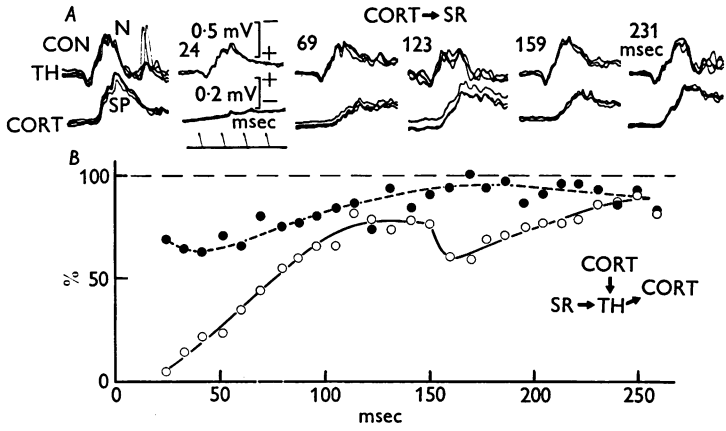

Fig. 7. Effect of cortical stimulation in conditioning the thalamic and cortical responses evoked by a contralateral afferent volley. In *A* the upper and lower traces show specimen records of thalamic N-waves and killed-end recording of spike potentials (SP) in thalamo-cortical fibres, there being responses to the SR volley alone (CON), and at the various intervals indicated in msec after conditioning by a single cortical stimulus to somato-sensory area I. All records are formed by superposition of several traces. The N and SP responses have been measured as percentages of the mean control values and are plotted in *B* against the corresponding CORT–SR intervals. ●, thalamic N-waves; ○, cortical spike potentials.

Since burst discharges were very effectively produced by cortical stimulation (Figs. 1*H*, 2*I*, 5*N–S*), cortical conditioning of the pathway from peripheral nerve to cortex would also be expected to exhibit separation of two phases of inhibition by a transient phase of excitation. For example, in the specimen records of Fig. 7*A* there was, at 24 and 69 msec after a conditioning cortical stimulus, a deep initial inhibition both of the thalamic N-wave (upper traces) and of the positive spike complex (SP, lower traces) led from the killed ends of the thalamo-cortical fibres. At an interval of 123 msec the testing response was superimposed on the first

burst discharge, as is shown by the irregularity of the base line preceding the thalamic record, and there was a relatively large potential in the lower trace as compared with that produced at a longer testing interval, 159 msec. The plotted curves of Fig. 7*B* show for the cortical SP responses (open circles) the time course of this relative recovery during the first burst discharge and the further depression following it. By contrast depression of the thalamic N-wave showed a smooth recovery that was almost complete at 170 msec. Since the thalamic N-wave in Fig. 7*A* (upper traces) is largely produced by synaptic excitation of the thalamic neurones by the lemniscal volley, the depression observed in the filled circles of Fig. 7*B* would be attributable to two inhibitory actions that the cortical stimulus would be expected to have: first, a transmission through the cuneate nucleus (Andersen, Eccles, Oshima & Schmidt, 1964) and, secondly, on the size of the EPSP which the lemniscal impulses generate in thalamic neurones. This latter effect is produced by the very large increase in conductance that would occur in the surface membrane of thalamic neurones during the large IPSP generated by the cortical stimulus (Andersen, Eccles & Sears, 1964).

Excitability of thalamic neurones

The factors influencing synaptic transmission from the medial lemniscus to the cortex can be investigated more selectively by employing as a test stimulus a brief electrical pulse delivered through a micro-electrode placed in close proximity to the ventro-basal thalamic synapses, as is diagrammatically shown in Fig. 8. The recording was from the killed ends of the thalamo-cortical fibres of the somato-sensory white matter. In the control specimen record in Fig. 8*A* the stimulus artifact was immediately followed by a sharp, positively directed spike (to be called α), which within 0·7 msec was followed by a second, more prolonged positive potential (to be called β). With this type of recording, such double spike responses were regularly produced in response to thalamic stimulation. With recording from the intact surface of the somato-sensory cortex, the double potentials were also regularly observed, but are less satisfactory for measurement, because they are diphasic (positive-negative) and the second spike suffers interference from the negative component of the first. It may be noted that Perl & Whitlock (1955) recorded similar brief spikes from the cortex when stimulating the thalamus or the radiation fibres therefrom, but with their relatively slow sweep speeds it was not possible to resolve the spike into the two components seen in Fig. 8*A*.

The α spike in Fig. 8*A* has such a brief latency that it must be due to direct excitation of thalamic relay cells or of their axons. Since the β spike occurs at just one synaptic delay later, it must arise because of direct

excitation of presynaptic fibres in the thalamus and the subsequent synaptic activation of thalamic neurones. The situation closely parallels that described by Renshaw (1940) when applying stimuli through needle electrodes in the central grey matter of the spinal cord and recording monophasically the spikes propagating out along a ventral root.

In the specimen records of Fig. 8*A* conditioning by an SR volley is seen to depress the production of both α and β spikes by the testing stimulus. The plotted points of Fig. 8*B* show that both α and β spikes

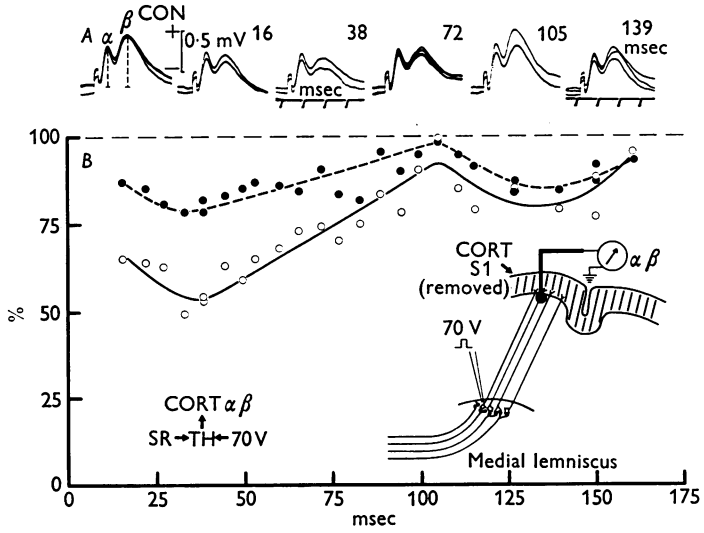

Fig. 8. Effect of a contralateral afferent volley in conditioning the excitability of thalamic neurones. As shown in the inset diagram, a brief current pulse was applied through a micro-electrode in the ventro-basal complex of the thalamus and there was unipolar recording from the killed ends of the thalamo-cortical fibres. The specimen records in *A* show the double α, β composition of the control (CON) and conditioned responses, the test intervals after conditioning by a single contralateral SR volley being given in msec. All records are formed by superposition of two or three traces. The α and β spikes are measured as percentages of the mean control values and are plotted in *B* against the corresponding intervals after the conditioning volley. A control calibration series (not illustrated) showed the effect on the α and β spikes of variation in the voltage driving the current through the stimulating electrode. Since there was an approximately linear relation over the range investigated, the percentages in *B* were approximate measures of the excitability changes, and this approximation was similarly shown to obtain for the percentages in Figs. 9–12. ●, CORT α; ○, CORT β.

exhibit a similar time course of depression and recovery beyond 100 msec. Again, the relative recovery of excitability at about 100 msec occurred at about the same time as the first burst discharge to the conditioning volley; and the second recovery occurred preparatory to the second burst

discharge. Throughout the whole sequence the β spike was depressed about twice as much as the α.

The relatively large size of the α spikes in Fig. 8 complicates the investigation of the β spike responses. Those thalamic neurones directly excited and giving the α response would be prevented by refractoriness from responding to the monosynaptic excitation that produces the β response. The inhibition of the α spike, as at 16 and 38 msec test intervals in Fig. 8*A*, thus increases the population of neurones available for giving the β spike.

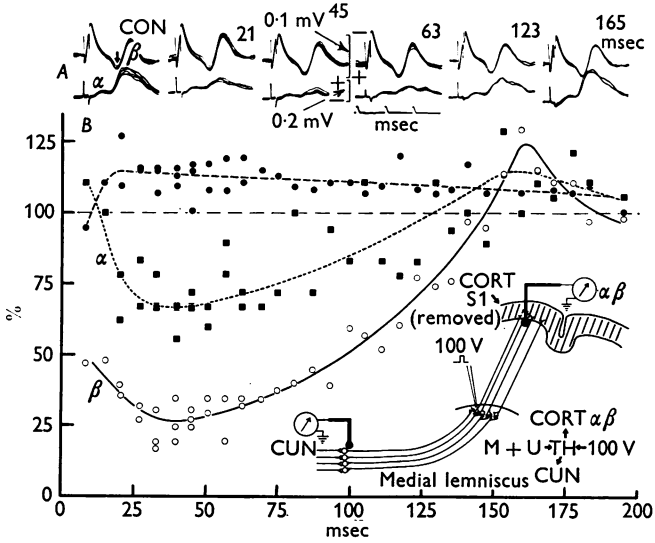

Fig. 9. Effect of a contralateral afferent volley in conditioning the excitabilities both of thalamic neurones and of the terminals of cuneo-thalamic fibres in the thalamus. Stimuli were applied through a micro-electrode in the thalamus as in Fig. 8, and, in addition to the recording of α and β spikes from the killed ends of the thalamo-cortical fibres, there was also simultaneous recording from the surface of the contralateral cuneate nucleus (see inset diagram) of the spike potentials propagating antidromically in the medial lemniscal fibres. In *A* are specimen records of the control (CON) responses and of responses at the indicated test intervals after conditioning by a combined M + U afferent volley. All records are formed by the superposition of several traces. In *B* these responses, measured as percentages of the mean control values, have been plotted against the testing intervals as in Fig. 8. ■, CORT α; ○, CORT β; ●, CUN.

The actual depression of the β spikes of thalamic neurones is thus underestimated in Fig. 8. This complication is much reduced in Fig. 9, where, because of the unfavourable location of the micro-electrode, relatively few thalamic neurones were directly stimulated to give the α spike. The depression of the β spike (open circles in *B*) was more than double that of the α (filled squares). Figure 9 also shows a peak of increased α and β

excitability at 165 msec, which was exactly synchronized with the first burst discharge. This synchronization is illustrated in Fig. 10, where the excitability tests giving the plotted curve were performed first and then the same micro-electrode was used for recording the potentials generated by the conditioning volley at exactly the same site in the thalamus. There is a very close correlation between the time courses of the α and β excitabilities and the potentials recorded from the site of stimulation.

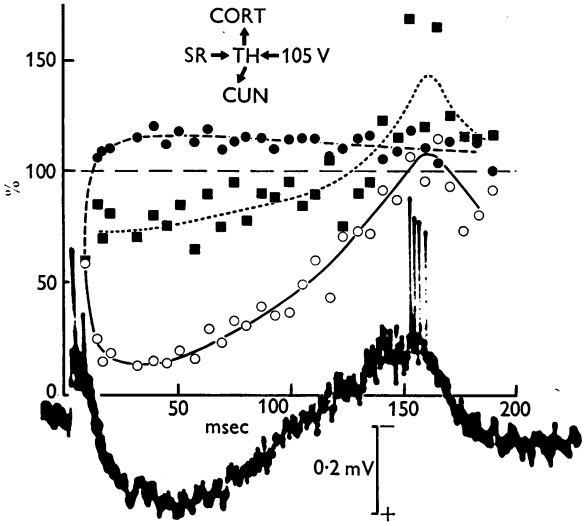

Fig. 10. Correlation of thalamic neurone excitability with evoked potentials in the thalamus. Plotting of α, β and presynaptic excitability as in Fig. 9, but in response to an SR volley and in another experiment. Superimposed on the graph at the same time scale there is the evoked potential in response to the same conditioning SR volley, recorded from the exact position at which the testing stimuli were applied, the stimulating electrode being employed for the recording. ●, CUN; ■, CORT α; ○, CORT β.

When the conditioning stimulus was applied to the somato-sensory area of the cortex, there was also a large depression of α and β excitabilities during the initial P-wave and the same recovery to a phase of increased excitability at the first burst response with a subsequent further depression (Fig. 11).

The depression of the α spike in Figs. 8, 9 and 10 shows that the conditioning volley has exerted a post-synaptic inhibitory action on the thalamic relay cells. The β spike would of course also be depressed by this post-synaptic inhibition, and conceivably the larger β depression could be attributable to a different incidence of the two testing excitations, direct and synaptic, on the thalamic cells. Alternatively, the β spike could be

additionally depressed by the presynaptic inhibition that arises as a consequence of depolarization of the presynaptic terminals (Frank & Fuortes, 1957; Eccles, Eccles & Magni, 1961; Eccles, Magni & Willis, 1962).

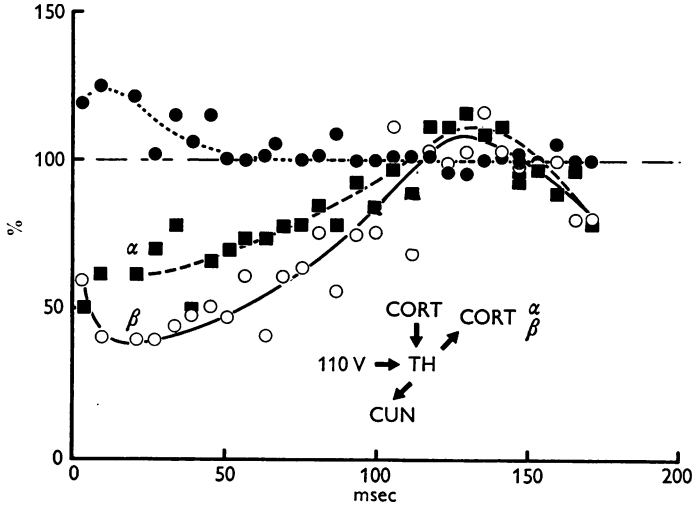

Fig. 11. Effect of cortical stimulation in conditioning the excitability both of thalamic neurones and of the terminals of cortico-thalamic fibres in the thalamus. Stimuli were applied through a micro-electrode in the thalamus as in Fig. 8 and the recording and plotting have been as in Fig. 9, the only difference being that the conditioning stimulus was applied to the somato-sensory cortex as in Fig. 7. ●, CUN; ■, CORT α; ○, CORT β.

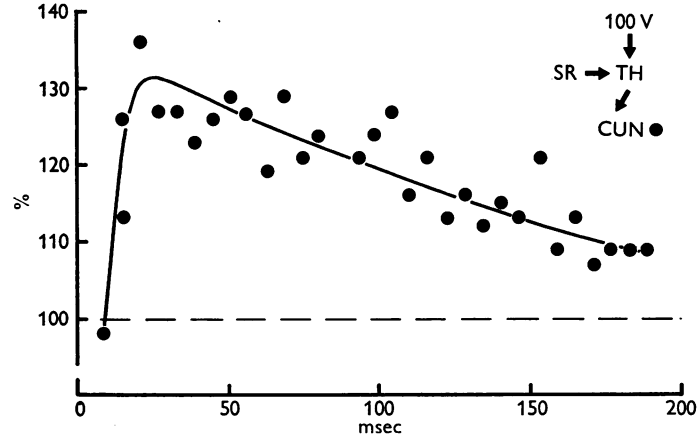

Fig. 12. Effect of a contralateral afferent volley in conditioning the excitability of the terminals of cortico-thalamic fibres in the thalamus. The experimental conditions and the plotting resembled that for presynaptic excitability in Fig. 9, but conditioning was by a single contralateral SR volley.

Excitability of presynaptic fibres in the thalamus. It has not been possible so far to use intracellular recording from the presynaptic terminals in order to measure presynaptic depolarization directly. A much simpler technique is to test for the depolarization indirectly by investigating the increased excitability thereby produced in the presynaptic fibres. This procedure has been fully described in relation to several investigations on presynaptic depolarization (Wall, 1958; Eccles *et al.* 1962; Eccles, Schmidt & Willis, 1963*a*, *b*).

In the upper row of the specimen records of Fig. 9*A* the thalamic stimulus is seen to evoke a large diphasic spike potential (positive-negative) in the cuneate nucleus. The latency of this spike is so brief (1·2 msec to onset of negative deflexion at arrow) that it must be attributed to antidromic activation of the cuneate neurones by a volley initiated in their thalamic terminals. The size of this diphasic spike may therefore be used as a measure of the number of thalamic terminals so excited; hence the excitability of these terminals is signalled by the size of the diphasic spike evoked by a fixed stimulus. For example, in the specimen records of Fig. 9, at 21 msec after a conditioning volley in the median plus ulnar nerves, the spike was much larger; and this was also observed at the longer testing intervals, but to a lesser degree. The time course of this increased excitability (filled circles in Figs. 9, 10) has the long duration characteristic of the presynaptic depolarizations responsible for presynaptic inhibition in the spinal cord and cuneate nucleus (Eccles, 1964; Andersen, Eccles & Schmidt, 1962).

In Fig. 12, conditioning by an SR volley is seen to be particularly effective in producing an increased excitability of the presynaptic terminals in the thalamus. The time course can be accurately defined and corresponds closely to that observed in other examples of presynaptic depolarization. Depolarizations of the size indicated by the excitability changes in Figs. 9, 10 and 12 would have a considerable inhibitory influence on the synaptic excitatory action of the lemniscal fibres terminating in the thalamus. The discrepancy observed between the depressions of the directly and synaptically evoked discharges of thalamic neurones in Figs. 8, 9 and 10 can thus be accounted for, at least to a considerable extent.

In Fig. 11 conditioning by cortical stimulation did not result in the prolonged increase in presynaptic excitability that is characteristic of presynaptic inhibition. However, there appeared to be a definite increase for about 50 msec. Further investigation is required before it can be assumed that this is indeed due to a presynaptic inhibitory action exerted by the cortex on the thalamic relay.

DISCUSSION

The α-excitability curves of Figs. 8–11 demonstrate that a conditioning afferent volley or cortical stimulus produces a depressed excitability of thalamo-cortical relay cells and that this depression has a time course corresponding closely to that of the extracellularly recorded P-waves, as is well illustrated in Fig. 10. Large and prolonged depressions of direct excitability of nerve cells may be due either to the after-hyperpolarization following a spike potential or to an inhibitory post-synaptic potential (Eccles, 1953, 1957). Marshall (1941) suggested the former explanation, but this has been disproved by recording from individual thalamic cells, where the hyperpolarization was found not to depend on the discharge of impulses by them (Purpura & Cohen, 1962; Andersen & Eccles, 1962; Andersen, Eccles & Sears, 1964); hence it can be concluded that the hyperpolarizing currents generated by the post-synaptic inhibition are responsible for the source that gives the P-wave.

The recovery of the relative negativity with the superimposed first burst discharge is matched by the recovery of α excitability, even to the extent of hyperexcitability in Figs. 9, 10; and again a further α depression was concurrent with the second P-wave and so on. The β-excitability curves display a larger depression than that of the α curves, but otherwise in Figs. 8–10 they show that the synaptic and direct excitabilities of the thalamo-cortical relay cells have very similar time courses of depression and recovery. Explanations of these observations and also of the various experimental observations of rhythmic burst discharges in Figs. 4 and 5 will be offered in the next paper after the mode of production of burst discharges has been considered.

The generation of P-waves by cortical stimulation (Figs. 1*G*, *H*, 2*I*) with the associated depressions of both α and β excitability (Fig. 11) suggests that the cortical stimulus is operating by the same pathway as the afferent volleys in producing the post-synaptic inhibition of the thalamo-cortical relay cells, and this will be supported by further evidence (Andersen, Eccles & Sears, 1964). The simplest hypothesis is that there is a recurrent inhibitory action mediated by inhibitory interneurones excited from axon collaterals of the thalamo-cortical relay cells, just as with the recurrent inhibition of motoneurones via Renshaw cells. The short latency of the P-waves in Fig. 1*G* (cf. Fig. 1*F*, Andersen & Eccles, 1962) indicates that possibly there is no more than one serial interneurone on this pathway.

The presynaptic hyperexcitability illustrated in Figs. 9, 10 and 12 was seen in five of the seven experiments where it was tested and usually was in the range of a 10–25 % increase. The depolarization responsible for this increase would presumably give presynaptic inhibition, and so explain,

at least in part, the greater depression of β than α excitability in Figs. 8–10. However, the level of hyperexcitability is relatively lower than that associated with presynaptic inhibition in the spinal cord (Eccles *et al.* 1962; Eccles *et al.* 1963*a*, *b*) and the cuneate nucleus (Andersen *et al.* 1964*b*). On analogy with these other sites of presynaptic inhibition it would be expected that the presynaptic depolarization would cause the production of a negative field potential, but in the thalamus this is submerged beneath the much larger positive potential generated by the postsynaptic IPSP. The neuronal pathways responsible for generation of this presynaptic depolarization will be considered in the next paper (Andersen, Eccles & Sears, 1964).

Since after a conditioning afferent volley the α and β excitabilities display a phase of relative recovery at 100–150 msec and then a subsequent further depression, the relative recovery in the somato-sensory pathway at about 120 msec (Fig. 6) can be attributed to events at the synaptic relay in the thalamus. The cuneate relay (Andersen, Eccles, Oshima & Schmidt, 1964) never displays the rhythmic sequences of recoveries and depressions that form such a feature of the thalamic relay; and in Fig. 7 the points plotting the time course of recovery of the thalamic N-wave would give an approximate time course of the cuneate inhibition, while the additional depression of the cortical SP-wave with partial recovery at 120–150 msec would be attributable to the thalamic relay.

SUMMARY

1. The somato-sensory pathway through the ventro-basal complex of the thalamus has been studied by three experimental procedures in an attempt to understand the rather complex neural mechanisms that are concerned with inhibition of thalamic transmission.

2. In agreement with previous investigations, an afferent volley produces in the thalamus a brief initial negative wave, followed by a prolonged positive wave that terminates after at least 100 msec in a negative wave that in turn ends abruptly in a second positive wave, and so on for several cycles. Similar sequences of positive and negative thalamic waves are also produced by antidromic activation of the thalamus from the somato-sensory cortex. On the negative waves there are often superimposed spike discharges, the so-called burst discharges, which in turn evoke cortical potentials. By both acute and chronic ablation experiments it was confirmed that these thalamic rhythmic responses are generated in the thalamus independently of thalamo-cortical connexions.

3. Transmission of a cutaneous afferent volley to the cerebral cortex has been inhibited either by a preceding afferent volley in the same or

another nerve or by a single stimulus to the somato-sensory cortex. In both conditions the inhibitory curve shows a period of depressed inhibition corresponding to the first negative wave of the rhythmic potential observed in the thalamus.

4. The excitability of the thalamo-cortical relay cells has been tested by brief electrical pulses applied through a micro-electrode inserted in close proximity to the thalamic synapses. In this way it has been shown that the positive waves produced both by afferent volleys and by cortical stimulation are due to post-synaptic inhibitory actions on the thalamo-cortical relay cells that depress their excitability, as tested both directly and mono-synaptically.

5. In addition cutaneous afferent volleys often produce a prolonged increase in excitability of presynaptic terminals in the thalamus, which is interpreted as being the presynaptic depolarization responsible for pre-synaptic inhibition.

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