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Inhibition at the T-Cells of the Spinothalamic Tract: A Neurophysiological Basis for Electrically Induced Analgesia[1] (38003)

RAIMOND EMMERS AND MARVIN I. RUDERMAN

Department of Physiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

It has been demonstrated that electrical stimulation of the dorsal columns of the spinal cord diminish the severity of pain in animals (1) and patients (2). Since the dorsal columns contain fibers which are relatively large in diameter, this observation appeared compatible with the hypothesis that large-diameter afferents activate a "gate control mechanism" (3) which determines the activity level of the spinothalamic tracts. Although the firing rate of certain cells in the spinal cord can be suppressed by stimulation of the dorsal columns (4), there is no definitive evidence that these are the cells of origin for the spinothalamic tracts. In fact, considerable uncertainty exists about the exact location of the spinothalamic transmission or T-cells. Some authors (4, 5) place them in laminae IV and V of Rexed (6), others (7) place them in laminae VI and VII. It is possible that these cells are not confined to any particular laminae of the spinal cord (8). Moreover, laminae IV–VII contain cells which give rise to other than spinothalamic tracts (9). Since, therefore, the spinothalamic T-cells cannot be identified by their anatomical location or by their response to peripheral stimulation, the use of some other method than those used previously for studying the dorsal column influence on the spinothalamic system appeared to be indicated. The design of such a method was made possible by the findings of several recent studies (10, 11, 12). These (a) described the thalamic termination sites of the spinothalamic tracts, (b) outlined a procedure for a functional localization of these termination sites in reference to the two regions (SI and SII) of the somesthetic thalamus, and (c) localized a synaptic junction between certain collaterals of the dorsal column fibers and the T-cells of the spinothalamic tracts. Since activation of the thalamic SII from peripheral receptors must pass via the spinocervicothalamic pathway (SCP) or via the spinothalamic tract (STT, Fig. 1), sectioning of the SCP should leave the T-cells of the STT as the sole relay of afferent excitations. Under these circumstances, stimulation of the dorsal columns (DC) prior to stimulation of the peripheral receptors should modify the firing of the spinothalamic T-cells. This in turn should be reflected in the evoked activity of the cells in SII.

Experiments of this design were carried out to answer the following questions: (a) Is afferent transmission via the STT to SII modified by a prior stimulation of the dorsal columns? (b) What is the duration of such a modification when a single stimulus is used to activate the dorsal column fibers? (c) Does the influence of the dorsal columns on the spinothalamic T-cells differ from such an influence on the T-cells of the SCP?

Materials and Methods. Twenty-three albino rats weighing over 500 g were used for the experiments. Animals of this size

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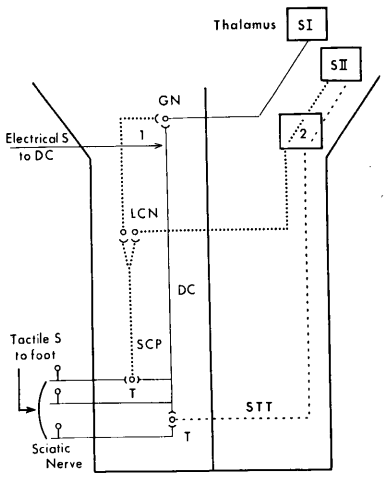
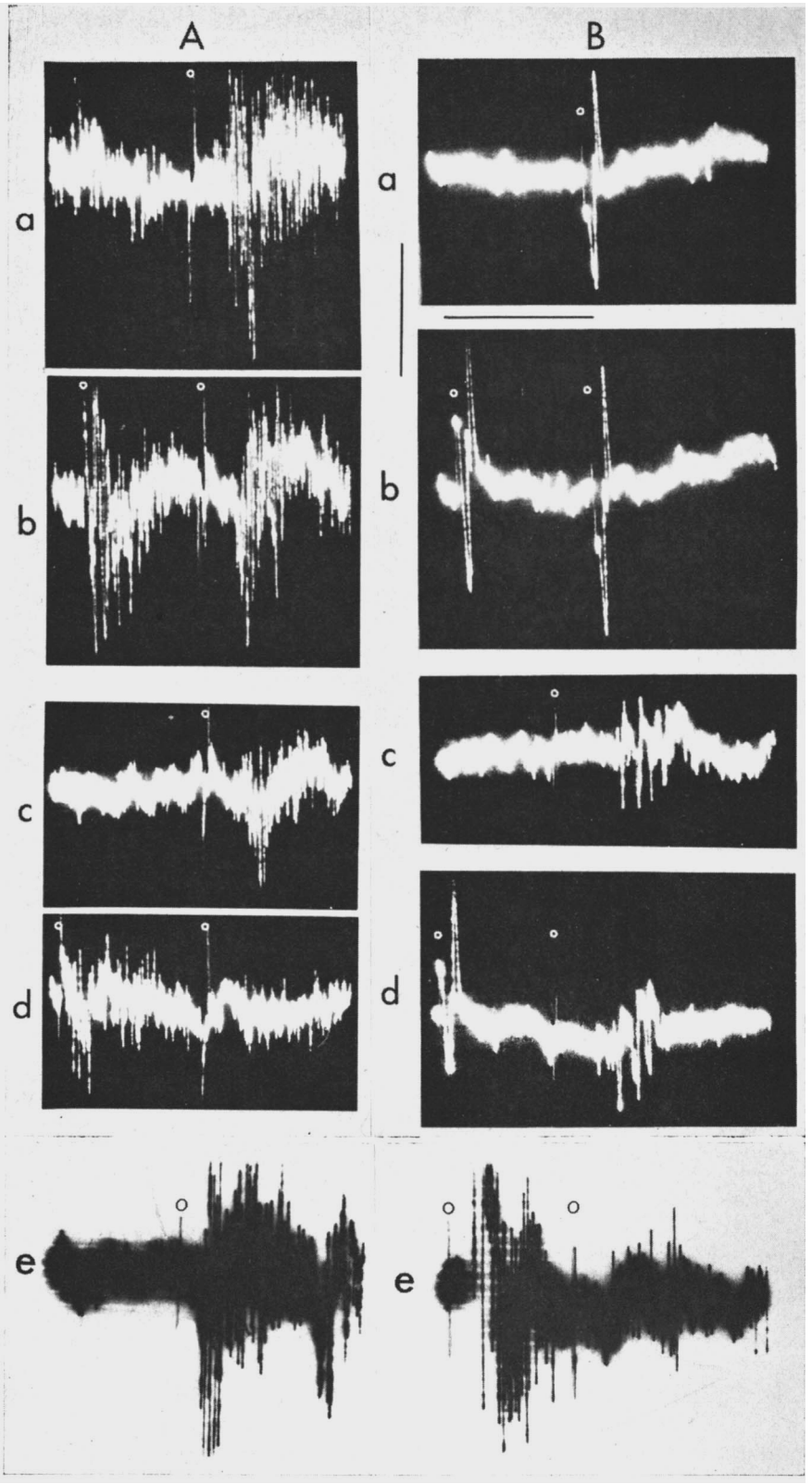


FIG. 1. A portion of a horizontal section of the spinal cord, the lower medulla, and the thalamus of a rat. The stimuli (S) were applied to sites 1 and 2 alone, or in combination with mechanical (tactile S) stimulation of the foot or electrical stimulation of the sciatic nerve to obtain responses in the thalamic regions SI and SII. DC, dorsal columns; GN, gracile nucleus; LCN, lateral cervical nucleus; SCP, spinocervical pathway; STT, spinothalamic tract; T, T-cells of the SCP and STT.

appeared to be less sensitive to barbiturate anaesthesia (45 mg/kg body wt) than animals of smaller size, and they survived the surgery without difficulty. A small opening was made in the skull at the intersection of coordinates placed 3.5 mm posterior to the bregma and 3.0 mm to the right of the midline. A laminectomy was performed to open the upper 3 vertebrae in the cervical region and the 8th, 9th, and 10th vertebrae in the thoracic region of the spinal cord. After the head of the animal was placed in the Stoelting Quadruple Stereotaxic Instrument, a steel microelectrode with a tip diameter of 10 μm was advanced with a micromanipulator to reach the hind leg projection region within the thalamic SI or SII. The method for localization of these regions has been described previously (12). It involves the mapping of peripheral projection fields for neurons of the somesthetic thalamus as the recording electrode is advanced ventrally in 0.3-mm steps (11). In SII the peripheral projection fields shift from snout to the front leg and finally to the hind leg, whereas in SI the neurons with their peripheral projection fields on the hind leg are encountered as soon as the recording electrode reaches the somesthetic thalamus. This region is situated approximately 1.2 mm rostrad and 0.2 mm medial to the hind leg projection region of SII. Mechanical and electrical stimuli were used. The mechanical stimuli were delivered to the skin with a rod encased in plastic. This rod could be moved electromagnetically by a trigger pulse in synchrony with the triggering of a Tektronix 502 oscilloscope. Another steel electrode, approximately 100 μm in tip diameter, was lowered under direct visual observation with a micromanipulator onto the gracile fasciculus approximately 3 mm caudad to the gracile nucleus. This was the site for stimulation of the dorsal columns as indicated diagrammatically in Fig. 1. Single pulses from a Grass S8 stimulator at 0.1-msec duration and 2.0 V were adequate to activate neurons in the hind leg projection region of SI via the gracile nucleus and those of SII via the spinal cord T-cells.

In four experiments afferent volleys were sent to the spinal T-cells of the SCP or the STT by applying single electrical pulses once every 2 sec to the sciatic nerve. The stimulus intensity (15 V, 0.5 msec) was adjusted to maximal; a further increase in the intensity of stimulation did not change the magnitude of the response. These experiments were performed to compare the effect of the gracile fasciculus stimulation on the excitation of the T-cells by two types of afferent volleys: one involving only those fibers which can be activated by light touch, the other involving the entire fiber spectrum of the sciatic nerve. Moreover, to keep synaptic excitability at a relatively high level, a mixture of urethane (400 mg/kg) and chloralose (40 mg/kg body wt) was used to anaesthetize these animals.

Results. As shown in Fig. 2Aa, mechanical stimulation of the animal's foot contralateral to the recording site in thalamic SI evoked multiunit activity with a latency of 10–12 msec. In this particular record the stimulus was delayed 50 msec. A nearly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identical response could be evoked in this thalamic region at a latency of 3 msec by applying an electrical pulse to the gracile fasciculus (Fig. 1, site 1). After this initial testing, the stimulus to the gracile fasciculus and the mechanical stimulus to the foot were applied at interstimulus intervals ranging from 0 to 200 msec.

No interference to the response evoked by the mechanical stimulus occurred when the electrical stimulus preceded the mechanical stimulus by more than 15 msec (Fig. 2Ab). At shorter than 15-msec intervals the conduction of the mechanical excitation encountered some interference in this pathway, and, depending on the intensity of the electrical pulse, responses to the mechanical stimulation were reduced in amplitude to zero.

Following this series of manipulation, the recording microelectrode was repositioned in the hind leg projection region of thalamic SII. Both electrical and mechanical stimuli were applied to the same sites and in the same manner as it was done while recording from SI. The records obtained from SII, however, differed conspicuously from those of SI.

A single mechanical stimulus applied to the animal's foot contralateral to the recording site in thalamic SII evoked multiunit activity with a latency of 18–22 msec (Fig. 2Ac). When this mechanical stimulus was preceded by an electrical pulse applied to the gracile fasciculus in the range of interstimulus intervals between 0 and 200 msec, the following sequence of events occurred. With an interstimulus interval from 0 to approximately 8 msec, the response evoked by the electrical stimulus was extended in duration by the response to the mechanical stimulus. Apparently, the T-cells, having been excited by action potentials induced antidromically in the gracile fasciculus, continued to be excited by action potentials which arrived orthodromically over some fibers of the sciatic nerve (Fig. 1). When the two stimuli were separated by a longer than 8-msec interval, the response showed two activity peaks. These became clearly separate responses at 10–15-msec interstimulus intervals. With longer than 15-msec intervals the response to the mechanical stimulus began to diminish in amplitude, and at interstimulus intervals between 25 and 60 msec it was abolished. Such an inhibition of the response to the mechanical stimulus at a 40-msec interstimulus interval is shown in Fig. 2Ad. Beyond 60-msec interstimulus separation, the response to the mechanical stimulus began to break through the inhibition, and at the interval of 200 msec no inhibition could be detected.

As the recording was done from cells located in the thalamic SII, inhibition of the response to mechanical stimulation could have taken place not only at the T-cells of the spinal cord but also at the cells of the thalamus. If inhibition were induced at the thalamic level, then dual stimuli applied to the SCP and the STT in the lower medulla at site 2 of Fig. 1 should reveal such an inhibition. However, the response evoked in the thalamic SII by the second electrical pulse (Fig. 2Ba) was not altered by the first (Fig. 2Bb) at any of the interstimulus intervals which showed inhibition when the stimuli were applied to the gracile fasciculus and the foot of the animal. Moreover, at these interstimulus intervals no inhibition was observed of the SII response evoked by mechanical stimulation of the animal's foot (Fig. 2Bc) when it was preceded by electrical stimulation (Fig. 2Bd) of site 2 of Fig. 1. Therefore, inhibitory mechanisms which abolished the response in SII to the mechanical stimulus

FIG. 2. Multiunit activity evoked in the rat thalamus. Stimulus artifacts are indicated by circles. Aa, stimulation: foot; recording: SI. Ab, stim.: site 1 of Fig. 1, then foot; rec.: SI. Ac, stim.: foot; rec.: SII. Ad, stim.: site 1 of Fig. 1, then foot; rec.: SII. Ba, stim.: site 2 of Fig. 1, rec.: SII. Bb, stim.: site 2 of Fig. 1, then repeat; rec.: SII. Bc, stim.: foot; rec.: SII. Bd, stim.: site 2 of Fig. 1, then foot; rec.: SII. Ae, stim.: sciatic nerve, rec.: SII. SCP was cut. Be, stim.: site 1 of Fig. 1, then sciatic nerve, rec.: SII. SCP was cut. Calibration lines at Ba: horizontal, 50 msec; vertical, 0.4 mV.

with a prior stimulation of the gracile fasciculus must reside at the junction between the collaterals of the gracile fasciculus of the dorsal columns, the T-cells, and the peripheral afferents to the T-cells.

After these results were obtained, a hemisection of the spinal cord was made at Th 9 ipsilaterally to the recording site in 6 of the 23 preparations. This eliminated the input into the thalamic SII via the STT. In four others the SCP was interrupted by cutting the dorsolateral funiculus contralateral to the recording site with a microdissecting hook at Th 9. Pairing of the electrical and mechanical stimuli was then resumed to determine whether inhibition had remained functional in the pathway left intact. Although the surgery tended to reduce the number of units which participated in the response, the onset and the duration of the inhibitory period were the same as in the intact animal. Moreover, there was no difference in the characteristics of inhibition at the T-cells of the SCP as compared to inhibition at the T-cells of the STT.

With 4 of the 23 preparations electrical stimulation of the sciatic nerve was used as an alternate method to excite the spinal T-cells. In two of these the STT was sectioned; in the others, the SCP was interrupted. The sciatic nerve was exposed at the hip, and neurons in the thalamic SII were localized which responded to pinching of the animal's toes with a series of burst-like firing. The sciatic nerve was placed between two Ag–AgCl wires separated by approximately 2 mm, and the nerve was ligated and cut peripherally. The electrical pulses evoked multiunit activity (Fig. 2Ae) which had a longer duration than the response evoked by the mechanical stimulus (Fig. 2Ac). Stimulation of the gracile fasciculus prior to the stimulation of the sciatic nerve by electrical pulses adjusted to maximal intensity for both (Fig. 2Be) abolished responses to the sciatic nerve stimulation. The interstimulus intervals at which total inhibition took place were the same (20–60 msec) for T-cells of SCP and STT, and differed little from that observed with mechanical stimulation of the animal's foot.

Discussion. Results of this study provide a definitive experimental evidence for the existence of a delayed postexcitatory inhibition at the T-cells of the STT and SCP. Although the existence of such an inhibition was postulated in part some time ago (3), its testing was delayed by lack of an adequate experimental design. Sampling of the activity of the spinal T-cells has been achieved in several studies (4, 5, 13) but their central projection sites remained obscure. Although certain criteria were employed to identify the T-cells which give rise to the SCP (13), the criteria were inadequate to separate these T-cells from others which form the dorsal spinocerebellar tract (9). Since in the present study the activity of the STT and SCP was followed in separate pathways up to the thalamus, the chance that excitation was transmitted to the recording sites by other than the T-cells of these tracts was obviated. As indicated, the transmission of the excitations was possible only during a relatively short period of time. Within 25 msec a severe inhibition developed. It must be remembered, however, that this inhibition was induced by simultaneous excitation of very many fibers of the dorsal columns. Under natural conditions activation of these fibers is asynchronous, and, therefore, it is less likely that such an inhibition will stop all firing of the T-cells. It is more reasonable to think that the effect of this inhibition is expressed in a reduction in the probability of the T-cell firing soon after their excitation via the dorsal column collaterals had taken place. Accordingly, burst-like activity should be particularly affected by the continuous reduction of firing probability. Since the number of spikes in burst-like firing is related to stimulus intensity (14), the concomitant sensory experience should become less intense. Consequently, it is relatively easy to understand how additional activity induced in the dorsal column collaterals by electrical stimulation (2) would result in a lesser activity of the STT. Moreover, since inhibition was found to exist at the T-cells which transmit excitations from whatever fiber types there are within the sciatic nerve, such a reduction in the activity of the SCP

and STT should induce not only analgesia but a local anaesthesia.

In this connection, it is interesting to note that inhibition at the first synaptic relay has been found to exist also in the trigeminal nuclei (15) and the duration of this inhibition is the same for many different sensory modalities. A similar phenomenon has been described with the gracile nucleus (16). The fact that it was not detected in the present study might have been due to the method used for the stimulation of the gracile fasciculus. An electrical pulse was applied in very close proximity to the synaptic junctions of the gracile nucleus. This might have disrupted the sequence of synaptic involvement necessary for the development of such an inhibition. The simple failure to excite neurons in the thalamic SI by peripheral stimulation within 15 msec after the stimulation of the gracile fasciculus was most likely due to the refractoriness of the gracile fasciculus fibers during their conduction of action potentials antidromically into the endings of the sensory receptors. Such an initial 15-msec inhibition can exist only under the specific technical arrangement of the experiments, and, therefore, it has no general physiological significance. On the other hand, inhibition at the synaptic junctions of the T-cells does not appear to be dependent upon the method of stimulation; it suggests the existence of a collateral circuit to the T-cells. An approximately 15-msec delay is imposed on action potentials which reach the T-cells via this collateral circuit. The last neuron in this circuit must be an inhibitory interneuron. The inhibition of the T-cells reaches its peak at approximately 25 msec following the activation of the collateral circuit.

The fact that inhibition at the first synaptic relay of a sensory path is a rather common finding renders it unlikely that the inhibition observed at the T-cells of the STT represents a unique coding mechanism for pain. If such a coding exists, as believed by some authors (4), it most likely represents only the first step in a more complex coding process. This process which should lead to the differentiation of somatic sensory modalities must take place at some other level of the central nervous system than the spinal cord or the medulla. The fact that separate and unique pulse codes exist for each modality of lingual afferents which are completed at the thalamic level (17) leads one to think that a similar process might take place with the coding of pain in the thalamic SII.

Summary. Rats were used to study the influence of dorsal column stimulation on the activity of those spinal cord cells which transmit peripheral excitations to the somesthetic thalamus via the spinothalamic tract (STT) and the spinocervicothalamic pathway (SCP). Since both of these paths terminate in the thalamic SII, separate transection of one of them left the other as the sole path of afferent excitations for reaching the thalamic recording site. This experimental design eliminated the uncertainty about the anatomical identity of the spinal cord transmission cells studied in experiments reported previously. Single electrical pulses applied to the gracile fasciculus of the dorsal columns inhibited the transmission of afferent activity via the SCP and STT when these pulses preceded the initiation of the afferent activity by 15–200 msec. This inhibition is most likely the basis for analgesia induced in patients by electrical stimulation of their dorsal columns. Since, however, a delayed postexcitatory inhibition has been recently observed to exist at the first synaptic relay of several sensory modalities, it is unlikely that the inhibition which exists at the T-cells of the STT represents a unique mechanism for the coding of pain. It is more reasonable to think that such a coding takes place at the thalamic level.

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