J. Physiol. (1975), **248**, *pp.* 725–739
With 1 plate and 6 text-figures
Printed in Great Britain

DESCENDING INHIBITORY INFLUENCES EXERTED BY THE BRAIN STEM UPON THE ACTIVITIES OF DORSAL HORN LAMINA V CELLS INDUCED BY INTRA-ARTERIAL INJECTION OF BRADYKININ INTO THE LIMBS

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(*Received 6 December 1974*)

SUMMARY

1. In order to study descending influences of the brain stem upon the transmission of nociceptive messages at the spinal level, the activities of lumbar lamina V dorsal horn cells, induced by intra-arterial injection of bradykinin into the limbs, were recorded in unanaesthetized cats in both decerebrate and temporary spinal states (reversible cold block applied at the thoracic level).

2. In the decerebrate state, the intra-arterial injection of bradykinin had little or no effect.

3. During the reversible spinalization, the effects of bradykinin were revealed or considerably enhanced. As described in a previous study, in the C1-transected cat, three types of effects were encountered: excitatory, inhibitory and mixed (inhibitory-excitatory).

4. These modifications observed after spinalization were generally associated with a large increase of the spontaneous firing rate.

5. These results emphasize, in the decerebrate cat, the importance of descending inhibitory controls exerted by the brain stem upon the transmission of nociceptive messages at the spinal cord level.

INTRODUCTION

During recent years, a great number of physiological studies have considered the properties of dorsal horn interneurones of the spinal cord and their possible implications on pain mechanisms.

Lamina V type interneurones present a special interest, since they are

* Chargée de Recherche à l'INSERM.

known to respond to activation of small diameter cutaneous fibres (Mendell, 1966; Hillman & Wall, 1969; Wagman & Price, 1969; Price & Wagman, 1970) and to visceral afferents (Pomeranz, Wall & Weber, 1968; Selzer & Spencer, 1969; Benelli, Besson, Guilbaud & Lombard, 1974). In the cat, some of these cells send their axons towards the brain in the spinocervical (Taub & Bishop, 1965; Fetz, 1968; Hongo, Jankowska & Lunderg, 1968; Brown & Franz, 1969; Bryan, Trevino, Coulter & Willis, 1973) and spinothalamic tracts (Dilly, Wall & Webster, 1968); in the monkey, recent studies have shown that some of them project centrally in the spinothalamic tract (Trevino, Coulter & Willis, 1973; Albe-Fessard, Levante & Lamour, 1974; Willis, Trevino, Coulter & Maunz, 1974) and spinocervical tract (Bryan, Coulter & Willis, 1974).

Moreover, several studies have demonstrated that the activities of lamina V type cells are continuously modulated by segmental and supraspinal controls, the latter mainly originated from cortical areas and brain-stem structures. Concerning the brain stem, Taub (1964) has shown that stimulation of the mesencephalic tegmentum induces strong inhibitory effects on the transmission through the spinocervical tract neurons. The former observation was confirmed on some dorsal horn (Wall, 1967; Hillman & Wall, 1969) and spinocervical cells (Brown, 1971) by comparing the spontaneous and evoked activities of each unit in both decerebrate and temporary spinal states. Brown (1971) pointed out that these inhibitory effects preferentially act on responses evoked by strong natural or intense electrical stimulation. Smilar observations have been made on responses of dorsal horn cells to noxious heat (Iggo, Handwerker & Zimmermann, 1974).

The aim of the present study was to consider brain-stem descending inhibitory effects on the activities of lamina V type interneurones induced by strong noxious stimuli: the intra-arterial injections of bradykinin into the limbs. Among numerous substances, known to induce nociceptive reactions in man and animal, bradykinin is considered as the most powerful (Armstrong, Dry, Keele & Markham, 1953; Burch & De Pasquale, 1962; Guzman, Braun & Lim, 1962; Sicuteri, Franchi & Fanciullacci, 1964; Lim, Miller, Guzman, Rodgers, Rodgers, Wang, Chao & Shih, 1967). Furthermore, this substance is released during the course of inflammatory processes in animals (Rocha e Silva & Antonio, 1960) and man (Chapman, Ramos, Goodell & Wolff, 1963; Eisen, 1969).

In a previous study in spinal cat (Besson, Conseiller, Hamann & Maillard, 1972), we found that lamina V type cells were preferentially and strongly affected by intra-arterial injections of bradykinin. This kind of stimulation used to investigate pain mechanisms seems to be particularly well adapted since we found that the latency and duration of unitary

responses were of the same order as those of painful sensations in man and pseudo-affective reactions in animals. In these experiments, by using reversible spinalization, we have studied the responsiveness of each lamina V type neurone to intra-arterial injection of bradykinin in both spinal and decerebrate states.

METHODS

This study was carried out on twelve cats weighing 2–3 kg. Animals were prepared under deep halothane anaesthesia, immobilized by gallamine triethiodide (Flaxedil), artificially ventilated and placed in a stereotaxic apparatus. An electrolytic decerebration was performed in the frontal plane $A + 4$ from the atlas of Jasper & Ajmone-Marsan (1954). This kind of decerebration was realized with seven parallel monopolar macro-electrodes which allowed coagulation of 168 points by three separate progressive descents in the same frontal plane. Systematic histological controls (Pl. 1) have indicated that this method was very efficient in obtaining a total decerebration. With the parameters used (5–8 mA during 30 sec) we checked that the coagulation did not exceed ± 2 mm in the antero-posterior plane. The anaesthesia was withdrawn at the end of this decerebration.

Rectal temperature, end-tidal CO_2 and arterial blood pressure were continuously monitored. Temperature was maintained at about 38° C, end-tidal CO_2 was kept between 4 and 4·5% and arterial pressure was always higher than 80 mmHg.

A first laminectomy was carried out from L4 to S1; then the dura mater was opened and the exposed cord was covered with warm mineral oil. The dura mater was retracted with stitches to form a sling and used to lift the cord slightly in order to reduce the effects of respiratory movements. To insert micro-electrodes, small openings were made in the pia using fine forceps under microscopic control.

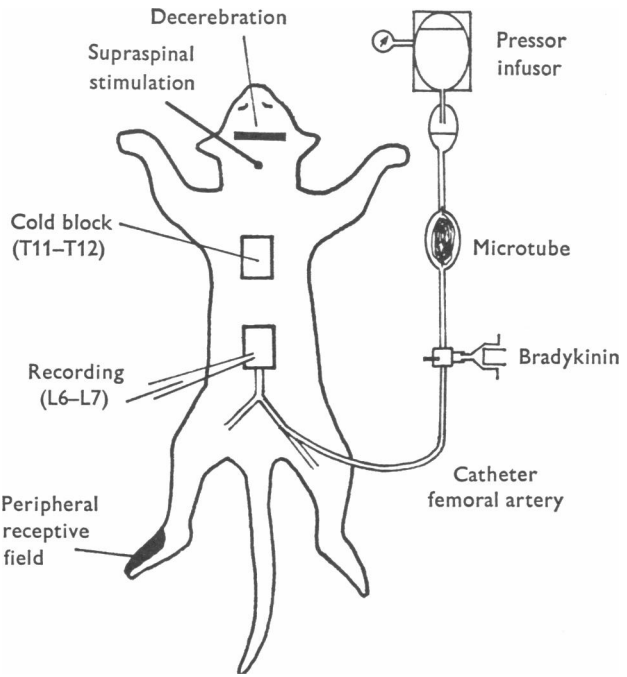
In order to practise a reversible spinalization by cooling the cord with Ringer ice, a second laminectomy was performed at T11–T12. The efficiency of the spinalization was controlled by considering the effects of a supraspinal stimulation on the activities of dorsal horn cells before and after cooling: a bipolar concentric electrode was implanted near the central inferior nucleus of the raphe and we checked that the inhibitory effects on lamina V cells by stimulation of this area (Le Bars, Menetrey, Conseiller & Besson, 1974) were totally suppressed during cooling.

The bradykinin was injected intra-arterially in the ipsilateral posterior limb: one femoral artery was catheterized with a fine polyethylene tube which was pushed to the aortic bifurcation for injection of bradykinin into the opposite posterior limb. All large vessels in the catheterized limb were ligated to prevent activation of receptors within that limb by the bradykinin injection. The permeability of the catheter was maintained by a continuous and very slow infusion of physiological fluid (2–4 ml./hr). Synthetic bradykinin (Sandoz) was injected through a three-way tap 10 μg in 1 ml. solution. Control injections were made with the identical volume of physiological fluid. The schema of the experiment is shown in Text-fig. 1.

Recordings were begun 3 or 4 hr after the elimination of the volatile anaesthetic. Extracellular unitary recordings were made in the L6–L7 segments using glass micro-electrodes filled with 3M-KCl, the resistance of which was 2 to 5 MΩ. The discharge frequency of units was recorded by means of a spike integrator (time base: 2 sec). Units the amplitude of which changed during bradykinin injection or after cooling the cord were eliminated. In some experiments, the dot-display technic was used to analyse the responses to intense electrical stimulation.

As in our previous study (Besson *et al.* 1972), lamina V type cells were

characterized, according to their electrophysiological properties as described by Wall (1967) and Hillman & Wall (1969). Additional anatomical localization was done by extracellular injection of pontamine blue (Godfraind, 1969).



Text-fig. 1. Schematic representation of the experimental procedures.

RESULTS

(*a*) *Spontaneous activity*

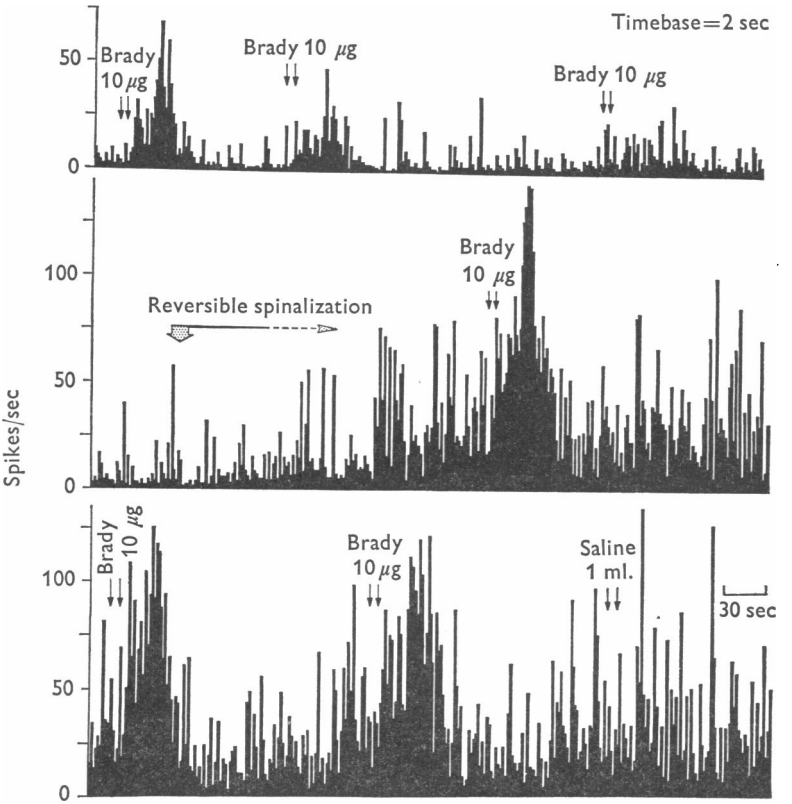
The suppression of descending inhibitory influences induced a large increase of the spontaneous activity of lamina V type cells. For the twenty-one studied cells, the mean value of the initial spontaneous activity in the decerebrate state was of $13{\cdot}0 \pm 3{\cdot}0$ spikes/sec. After reversible spinalization, the mean value was increased to $32{\cdot}5 \pm 6{\cdot}5$ (to suppress) spikes (250 % of the initial value; $t_{18} = 3{\cdot}74$: $P < 0{\cdot}01$). This increase of the spontaneous firing rate was observed for the majority of cells since only five out of twenty-one were unaffected by the spinalization. There was no relationship between the level of the spontaneous activity in decerebrate state and its increase after spinalization.

In Text-fig. 2 continuous recording of 20 min shows that these modifications appeared relatively quickly after the cooling (less than 3 min).

(*b*) *Modifications induced by intra-arterial injection of bradykinin*

General findings

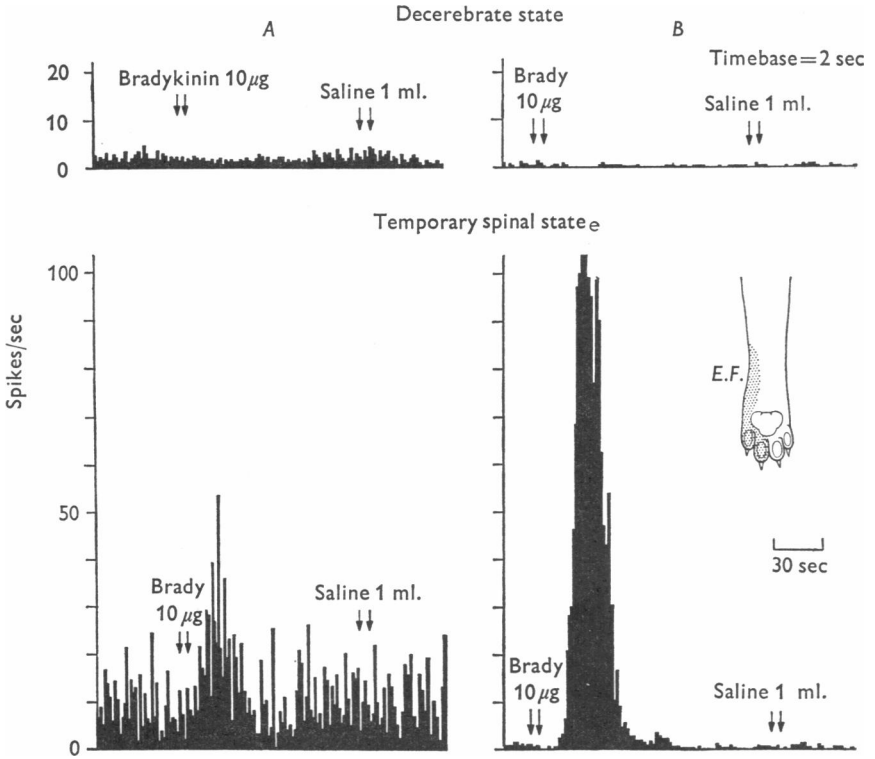
In the 'decerebrate state', only five cells out of twenty-one were affected by bradykinin injection. Among these five affected cells, four were excited and one inhibited; but, as shown in Text-figs 2 and 6, these modifications were of minor importance and not easily reproducible. By



Text-fig. 2. Excitatory effects of bradykinin (Brady) on a given lamina V cell in decerebrate and temporary spinal state. In the decerebrate state (upper trace), the excitatory effects are of minor importance and not easily reproducible. After reversible spinalization which induces a large increase of the spontaneous firing rate the responses to bradykinin are considerably enhanced and well reproducible. Injection of physiological fluid does not induce significant variations in the firing rate.

contrast, in the 'spinal state', the effects of bradykinin injections are revealed or enhanced since sixteen cells out of twenty-one were affected. Among these sixteen cells, nine were excited, four inhibited and three

showed a mixed inhibitory-excitatory effect. In the spinal state, the modifications obtained after bradykinin injections were easily reproducible. When the duration of a cell recording was long enough to practise several successive reversible spinalizations, the modifications observed between the decerebrate and the spinal states were always similar. To clarify the presentation of our results, the cells were classified according to their responses in the 'spinal state'.

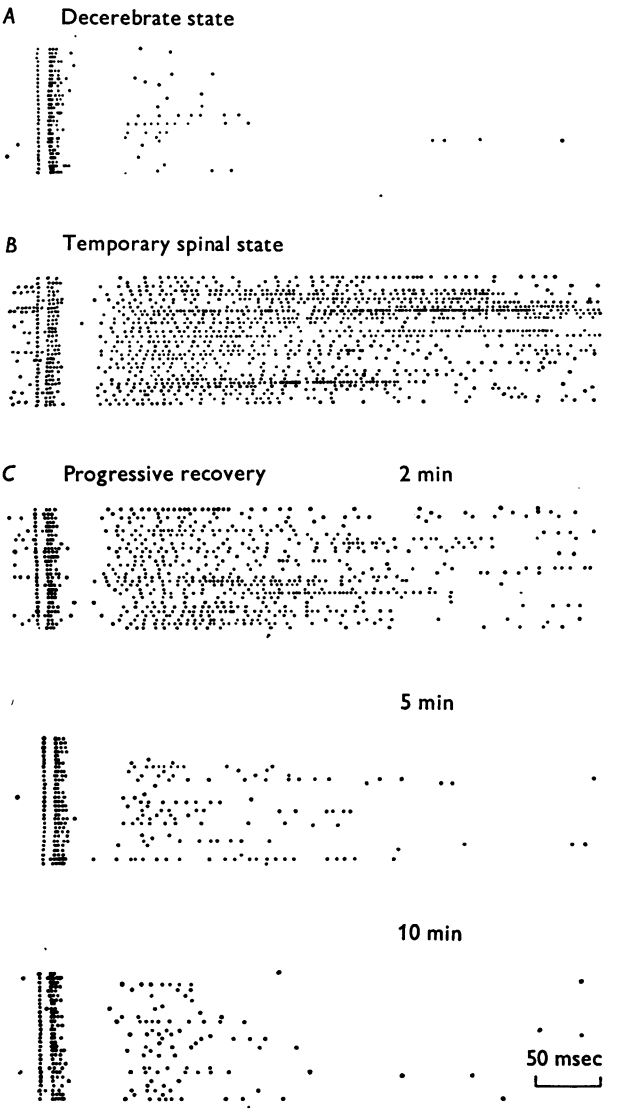


Text-fig. 3. For these two lamina V type cells the effects of bradykinin are totally absent in the decerebrate state. Large excitatory modifications appear in the temporary spinal state. In *A*, these modifications are associated with an increase of the spontaneous firing rate, while, in *B*, the level of the spontaneous activity is unaffected. (*EF*, excitatory receptive field.)

Excitatory effects (nine out of twenty-one cells)

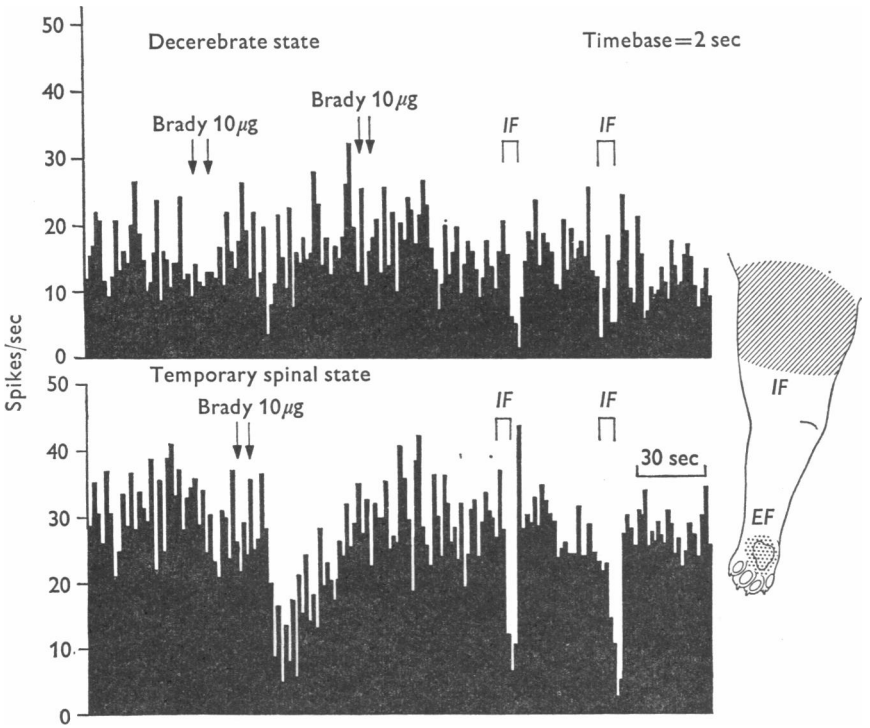
Among these nine cells, only one was activated in the 'decerebrate state'; in this case (Text-fig. 2), the increase of spontaneous activity induced by the spinalization is associated with an enhancement of the bradykinin evoked excitatory response. The evoked excitatory effects

observed in the eight other cells only appeared after the spinalization; in six cases, this appearance of large activation was associated with an increase of spontaneous firing rate (Text-fig. 3*A*), while, in two cases, it was not (Text-fig. 3*B*).



Text-fig. 4. Dot display analysis of the responses of a given lamina V type cell to intense electrical stimulation within the cutaneous receptive field in both decerebrate and temporary spinal state.

The excitatory effects observed in these nine cells appear not to be connected with the level of the spontaneous activity observed in both decerebrate and spinal states. In the spinal state, the mean latency of the excitatory effect was 22 sec and its mean duration was 62 sec. Although the effects of bradykinin were easily reproducible for a given cell (Text-fig. 2), we must point out that the degree, the latency and the duration of activation show a great variability between cells.

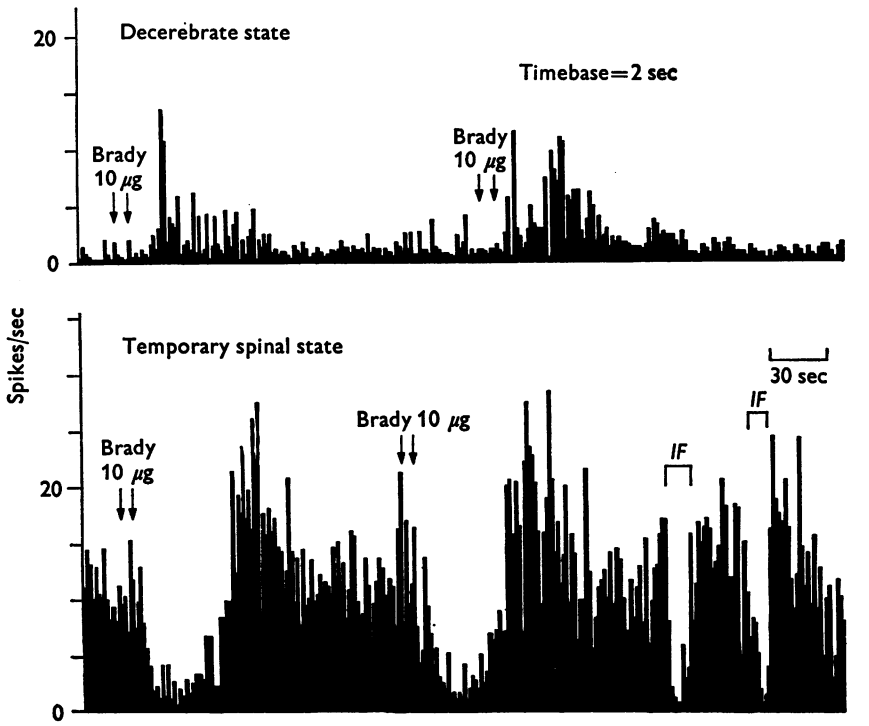


Text-fig. 5. Inhibitory effects (in the temporary spinal state) induced on a lamina V type cell by intra-arterial injection of bradykinin. As shown in the drawing, this unit has a wide inhibitory peripheral field (*IF*, inhibitory receptive field; *EF*, excitatory receptive field).

In several cases, the importance of descending inhibitory controls upon the activity of lamina *V* type cells has also been observed on excitatory response elicited by supramaximal electrical stimulation applied in the centre of the cutaneous receptive field. As shown in Text-fig. 4*A* in the decerebrate preparation, this kind of stimulation evoked a short latency response followed by a late component of few and inconstant spikes. After spinalization (Text-fig. 4*B*), the short latency response is unaffected, but the late component is considerably enhanced.

Inhibitory effects (four out of twenty-one cells)

The firing rate of these cells was not significantly modified by the bradykinin injections in the decerebrate state. Clear inhibitory effects appeared after spinalization (Text-fig. 5). In three cases, this effect was associated with an increase of the spontaneous activity. For these four inhibited cells, the mean latency of the inhibitory effect was of 15 sec and its mean duration of 55 sec. It is of interest to note that, in all these cases, a clear and wide ipsilateral inhibitory receptive field could be found in the spinal state by using cutaneous natural stimulation; this inhibitory field was always more proximally located than the excitatory one.



Text-fig. 6. Diphasic responses of a lamina V cell. In the decerebrate state, there is only a weak excitatory effect. In the temporary spinal state, an inhibitory effect of long duration preceded a late excitation.

Inhibitory-excitatory effects (three out of twenty-one cells)

In the decerebrate state, these three cells presented weak excitatory responses to bradykinin injection (mean latency: 28 sec; mean duration: 30 sec). After spinalization, the spontaneous firing rate of these units was greatly enhanced and the injection of bradykinin elicited a strong

inhibitory effect followed by a late excitation (Text-fig. 6). The mean latency of the inhibitory effect was 16 sec and its mean duration was 63 sec. In these cases, a clear inhibitory receptive field was observed in the spinal state.

Unaffected cells (five out of twenty-one cells)

These cells were unaffected by bradykinin in both decerebrate and spinal states. Nevertheless, the spontaneous activity of three of them was clearly increased by spinalization.

DISCUSSION

I. Before considering our results in detail, it seems necessary to discuss the value of using bradykinin to study structures of the central nervous system involved in the transmission of painful messages.

Mense & Schmidt (1974) have shown that a great number of group IV afferent units from muscle are activated by intra-arterial injections of bradykinin. Other studies on peripheral cutaneous afferent fibres have emphasized the fact that this drug excites not only both small myelinated and non-myelinated fibres, but also fibres driven by stimulation of low threshold slowly-adapting mechanoreceptors (Fjällbrant & Iggo, 1961; Beck & Handwerker, 1974). Therefore, these authors have concluded that the intra-arterial injection of bradykinin cannot be considered as a 'specific nocuous stimulant'.

But, in our opinion, the concept of a 'specific nocuous stimulant' is a purely psychophysiological one. Therefore, any information on the fibre types activated by bradykinin, or any other stimulus considered to be nociceptive, has no bearing on whether or not that stimulus is purely nociceptive. This question can only be answered by experiments in psychophysiological domain, and, even with this approach, it is difficult to define such a pure nociceptive stimulus; this is well indicated by the multiplicity of terms describing painful sensation in humans.

Nevertheless, among various noxious stimulations used, it appears, from various reports in humans, that bradykinin is, on one hand, one of the most powerful and on the other hand, one of the most specific noxious stimuli. Moreover, we found that the latency and duration of cell responses to intra-arterial injection of bradykinin are similar to the latency and duration of pain sensation in man when using such a stimulus (Besson *et al.* 1972; Guilbaud, Besson, Oliveras & Wyon-Maillard, 1973; Besson, Guilbaud & Lombard, 1974; Benelli *et al.* 1974). Therefore, fibres that are activated by this drug and their interactions become important in the study of the physiology underlying painful sensation. Indeed, the messages carried by the different fibre types have to be integrated at one or more

levels of C.N.S. before being recognized as noxious messages. Thus, to study the effect of nociceptive stimulation from a physiological point of view, an important point is to consider the output of cells involved in the transmission and the integration of nociceptive messages. One such integrative mechanism has been proposed by Melzack & Wall (1965) to exist in the trigger cells of the spinal cord dorsal horn.

II. From our results, it appears that, in the decerebrate cat, responses of lamina V type cells to the nociceptive stimulation induced by intra-arterial injection of bradykinin are strongly inhibited by the influence of brain-stem structures. Indeed, in the decerebrate state, only five of the twenty-one cells were affected by bradykinin and, in these cases, the observed modifications were of minor importance and gradually faded. The effects of bradykinin are considerably enhanced or revealed after the suppression of descending inhibitory impulses by reversible spinalization and, in this state, a great number of cells (sixteen out of twenty-one) were affected. As previously observed in the Cl, transected spinal cats (Besson *et al.* 1972), three types of effects were encountered in the temporary spinal state: excitatory, inhibitory and mixed (inhibitory-excitatory). Although the number of cells studied in the present work is relatively small, twenty-one, we must emphasize the fact that the sample is representative of lamina V cells responses to bradykinin, since the proportions of each kind of modifications are of the same order as those found on a large number of cells in the Cl transected cat (Besson *et al.* 1972).

These modifications observed after spinalization are generally associated with an important increase of the spontaneous firing rate. This observation agrees with the findings of Wall (1967) on some dorsal horn interneurones and those of Brown (1971) on some spinocervical tract cells. Furthermore, when the cord was blocked, we generally observed an expansion of excitatory receptive field as previously described by Wall (1967).

(*a*) The brain stem exerts powerful inhibitory effects upon the excitatory responses of lamina V cells to bradykinin injections. Indeed, in the decerebrate state, only one cell was weakly excited, while nine were strongly activated by such an injection in temporary spinal state. For several cells we checked that responses elicited by innocuous stimulation (touch) were similar in both decerebrate and spinal states. As in the Brown studies (1971), the selectivity of the inhibitory controls was also observed on responses to supramaximal electrical stimulation, since inhibitory descending control does not affect early component while it dramatically reduces the late one. This inhibitory effect on impulses driven by thin fibres has been also observed on noxious impulses elicited by radiant noxious heat stimulation (Iggo *et al.* 1974; Zimmermann & Handwerker, 1974). These authors pointed out 'that the discharges of class 2

neurones during mechanical skin stimulation are affected to a much lesser extent by the cold block of the spinal cord.'

This preferential effect of descending inhibitory controls from the brain stem seems to be a general rule since we have previously found that the stimulation of dorsal raphe nucleus preferentially depresses lamina V cells activities induced by strong natural cutaneous stimulations (Oliveras, Besson, Guilbaud & Liebeskind, 1974).

From all these data, it clearly appears that the stronger the peripheral stimulation inducing trigger cells output is, the more powerful are the brain-stem inhibitory controls. The fact that the excitatory effects of bradykinin are absent or almost suppressed in the decerebrate state indirectly argues for the minor part of the activation of large fibres by this substance, in the final trigger cell output.

(*b*) The descending influences of brain-stem structures are also acting upon the inhibitory responses to bradykinin injection. These responses, which only appear in the temporarily spinalized cat, are always associated with the existence of a clear peripheral cutaneous inhibitory receptive field which is almost non-existent in the decerebrate state. This finding agrees with those of Brown (1971) who mentioned that this inhibition is more readily seen in spinocervical tract units in the spinal preparation than in the decerebrate one. Within such fields, either light repetitive natural stimulations (touch) or strong natural stimulation (pinch) are able to induce inhibitions of the firing rate. Thus, the inhibitory effects of bradykinin may result from activation of thin and large peripheral fibres of the wide inhibitory field, which are able to induce post-synaptic inhibition on lamina V type cells (Hongo *et al.* 1968; Besson, Catchlove, Feltz & Le Bars, 1974). The proximal location and the large size of the peripheral inhibitory field could explain the pre-eminence of inhibitory effects on these cells. Indeed, with our modalities of injection, bradykinin reaches the inhibitory field before the excitatory one, the stimulation of which could be masked. This hypothesis seems to be confirmed by the fact that we found, in the spinal state, some mixed inhibitory-excitatory responses, where the former always preceded the latter.

(*c*) From these results, it appears that both excitatory and inhibitory responses to bradykinin intra-arterial injections are, in the decerebrate preparation, strongly depressed by impulses descending from the brain stem. Several studies indicate that this descending inhibition seems to be of a pre-synaptic nature (Taub, 1964; Wall, 1967). The preferential control observed on responses to strong stimulation (pinch, noxious heat, bradykinin) seems to be in good agreement with this hypothesis. Nevertheless, only intracellular recordings could determine the exact nature of this inhibition.

From a general point of view, these data underline the importance of brain-stem structures in the control of painful messages. Such controls have recently been emphasized by behavioural and pharmacological experiments: stimulation of peri-aqueductal gray matter in the rat (Reynolds, 1969; Mayer, Wolfle, Akil, Carder & Liebeskind, 1971; Mayer & Liebeskind, 1974) and of raphe nuclei in the cat (Oliveras *et al.* 1974) induces a powerful analgesia, while the analgesic effect of morphine has been attributed to be in part due to an increase of descending inhibitory influences from brain-stem structures (Takagi, Matsunara, Yanai & Ogiu, 1955; Satoh & Takagi, 1971; Vogt, 1974).

This work was supported by CNRS (E.R.A. 237). The synthetic bradykinin was kindly supplied by Sandoz Laboratories (Basel, Switzerland).

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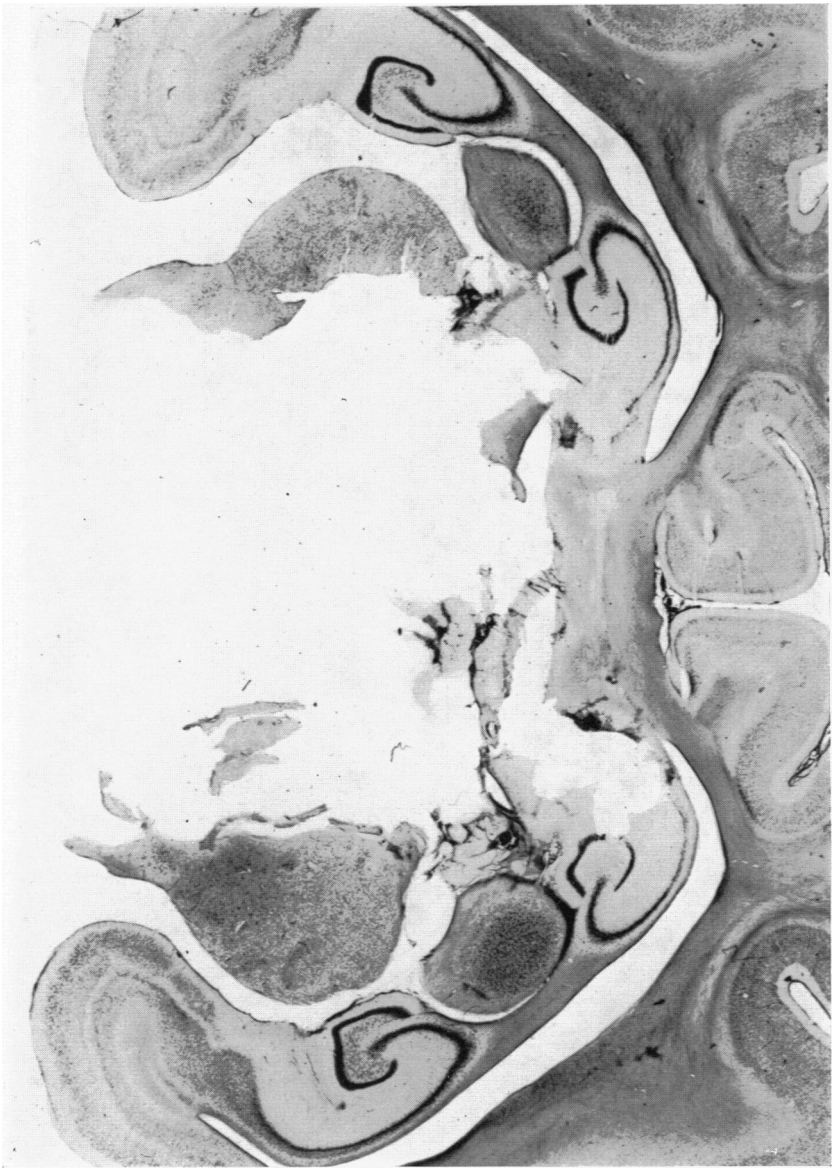

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EXPLANATION OF PLATE

Histological section in frontal plane, anterior 4, showing the decerebration obtained by electrolytic coagulation.