*Journal of Physiology* (1993), **466**, *pp.* 191–211
*With 11 figures*
*Printed in Great Britain*



# CONVERGENCE IN SEGMENTAL REFLEX PATHWAYS FROM NOCICEPTIVE AND NON-NOCICEPTIVE AFFERENTS TO α-MOTONEURONES IN THE CAT

BY H. STEFFENS AND E. D. SCHOMBURG
*From the Institute of Physiology, University of Göttingen, D-3400 Göttingen, FRG*

(*Received 27 May 1992*)

SUMMARY

1. Reflex interaction between nociceptive and non-nociceptive segmental afferents was investigated by testing for spatial facilitation of postsynaptic potentials (PSPs) in α-motoneurones recorded in anaemically decapitated, high spinal cats. Nociceptive segmental afferents were activated by applying noxious radiant heat to the skin. Non-nociceptive skin mechanoreceptors were activated by puffs of air. Non-nociceptive skin, joint and group I–III muscle afferents were stimulated by electrical pulses delivered to various nerves.

2. Conditioning by stimulation of nociceptive afferents facilitated transmission in various ipsilateral segmental pathways. Such spatial facilitation occurred in both excitatory and inhibitory pathways. Pathways that were facilitated included those activated by low to medium threshold cutaneous afferents, joint afferents, and group Ib and II muscle afferents.

3. In contrast, monosynaptic EPSPs evoked by stimulating ipsilateral group Ia muscle afferents did not show spatial facilitation but rather inhibition during conditioning stimulation of nociceptive afferents. Spatial facilitation of reciprocal group Ia IPSPs was rare and small if it occurred.

4. Pathways activated by cutaneous and group II muscle afferents were depressed by contralateral stimulation of nociceptive afferents.

5. We conclude that spatial facilitation observed between nociceptive and non-nociceptive afferents results from a convergence of inputs on common interneurones in the reflex pathways to α-motoneurones. Therefore nociceptive afferents have to be regarded as constituents of flexor reflex afferents (FRAs) and may add a specific nocifensive function to the FRA system.

## INTRODUCTION

Since the work of Sherrington (1903), the flexion reflex, i.e. withdrawal of the affected limb from contact with injurious agents (Creed, Denny-Brown, Eccles, Liddell & Sherrington, 1932), has been regarded as the fundamental spinal motor action of nociceptive afferents (for a review see Willis, 1985). However, a wide group of non-nociceptive afferents of different origin (low to medium threshold cutaneous

receptors, medium to high threshold muscle endings, joint receptors) may also evoke the flexion reflex under particular conditions (Eccles & Lundberg, 1959). These afferents which use common segmental interneuronal systems and ascending pathways have been described as 'flexor reflex afferents' (FRAs; Eccles & Lundberg, 1959; Holmqvist & Lundberg, 1961); but it has been stated that alternative reflex pathways to motoneurones could also be used by these afferents (Eccles & Lundberg, 1959). It has been suggested that the FRA system forms a multisensorial feedback system channelling information from a variety of receptors that are activated during a movement (Lundberg, 1979; Lundberg, Malmgren & Schomburg, 1987*c*). The relationship of nociceptive afferents to this unspecific FRA system was not clear (cf. Lundberg, 1982). Nociceptive afferents converge with low threshold mechanosensitive cutaneous afferents in the reflex effects elicited in motoneurones (Schomburg & Steffens, 1986); however, it remains uncertain if nociceptive afferents contribute to the multisensorial FRA system. Therefore we tested for spatial facilitation of PSPs to investigate a possible convergence between nociceptive and non-nociceptive afferents of different origin onto common interneurones in reflex pathways to $\alpha$-motoneurones. This technique has been successfully used for the investigation of convergence between segmental reflex pathways from different types of muscle and non-muscle afferents and between descending and segmental pathways to $\alpha$-motoneurones (for reviews see Lundberg, 1979; Baldissera, Hultborn & Illert, 1981; Schomburg, 1990; Jankowska, 1992).

## METHODS

*General procedures.* The experiments were carried out on thirty-four adult cats weighing 2·9–5·1 kg. Under general ether–halothane–nitrous oxide anaesthesia the cats were anaemically decapitated by ligature of the carotids and their main branches, and of the ascending vertebral arteries. An irreversible interruption of the spontaneous respiration resulted from this procedure together with persistent large and non-reacting pupils. These effects were taken as a sign of the completion of anaemic decapitation.

To prove the reliability of the procedure, in a former series of experiments 100 ml of an Evans Blue solution (0·5 g (100 ml)$^{-1}$, 2000 i.u. heparin added) was infused over a period of 3 min. The cat was killed and dissected 5 min after the infusion. In contrast to spinal structures and the muscles of the body and limbs, no dye was found within the superficial (pial) and deep brain vessels (for further details see Kniffki, Schomburg & Steffens, 1981).

After the anaemic decapitation the cat was artificially ventilated, spinalized at C1 and paralysed with pancuronium bromide (Pancuronium 'Organon', about 0·15 mg kg$^{-1}$ every hour I.V. as required). End-expiratory $CO_2$ concentration of 4% was regulated via the respiratory volume. The arterial blood pressure was maintained above 80 mmHg, if necessary by infusion of a dextran solution. Rectal temperature was maintained close to 37–38 °C.

*Preparation.* A laminectomy was performed to expose the lumbosacral spinal cord. The ventral roots L5–S1 on the left side and the following nerves of the left hindlimb were sectioned and mounted for electrical stimulation (abbreviations and number of recorded motoneurones of the corresponding muscles are in parentheses): quadriceps (Q), posterior biceps and semitendinosus (PBSt, 43), anterior biceps and semimembranosus (ABSm, 25), flexor digitorum and hallucis longus (FDL, 8), plantaris (Pl, 6), or FDL and Pl together (FDL–Pl, 1), peroneus longus, brevis and tertius (SPM, 1), tibialis anterior and extensor digitorum longus (DP, 1), gastrocnemius and soleus (GS, 42, partly divided into lateral gastrocnemius and soleus, LGS, and medial gastrocnemius, MG), plantar section of the tibial nerve which is a mixed motor (fibres to intrinsic foot muscles) and cutaneous (skin innervation of the foot pads) nerve (Tib, 4), suralis (Sur, partly divided into its medial, mSur, and lateral, lSur, branch), saphenous (Saph), cutaneous part of the superficial peroneal nerve (SPC), and the medial nerve to the knee joint (joint). In each experiment one of the cutaneous

nerves (mSur, SPC, Tib or Saph) remained intact for mechanical and radiant heat stimulation of skin receptors.

*Stimulation.* Electrical stimulation was performed with single rectangular pulses (duration 0·1 ms); stimulus strength is expressed in multiples of threshold ($T$) for the nerve. Mechanical and radiant heat stimulation were applied to the cutaneous receptive field of the intact nerve. Radiant heat of a 150 W projector bulb was focussed on a 1 $cm^2$ area of shaved skin. Skin surface temperature in the centre of the focus was measured with a sensor (Cu–CuNi, 0·3 $mm^3$) and was kept constant by an electronic feedback controller (Beck, Handwerker & Zimmermann, 1974). Standard testing was performed with the stimulus temperature between 48 and 53 °C; however, at the end of an experiment, the stimulus temperature was raised to 60–63 °C for a few stimuli. Stimuli were applied to the following areas: (1) the lateral part of the foot (SPC intact), (2) the dorsum of the foot (mSur), (3) the medial part of the foot and medial surface of the leg (Saph), and (4) the central pad of the foot (Tib). Mechanical skin stimulation was performed with an air jet (outlet diameter 1 mm), pulses blowing tangentially to the hairy skin in the receptive field of the intact nerve (duration 10 ms). The pressure of the air jet system was $2{\cdot}3 \times 10^5$ N $m^{-1}$. Air jet pulses were formed by an electronically controlled magnetic valve.

*Recording.* Intracellular recordings were made from 129 lumbar $\alpha$-motoneurones (for distribution concerning the muscles see above) in the L7 spinal segment using 2 M potassium citrate or 3 M KCl microelectrodes. Continuous DC recordings (bandwidth 0–10 kHz) of the membrane potential were made during mechanical or radiant heat stimulation. Motoneurones were identified by antidromic invasion following electrical stimulation of the ventral roots and monosynaptic responses to stimulation of group Ia afferents of a muscle nerve. To separate the fraction of the PBSt motoneurones from that of ABSm motoneurones, all motoneurones that received distinct (more than 0·5–1·0 mV) monosynaptic EPSPs from the ABSm nerve were classified as ABSm motoneurones, even if they received monosynaptic EPSPs from the PBSt nerve.

To record extracellular field potentials, we removed the tip of the electrode to a point directly outside the recorded motoneurone where the membrane potential went to zero.

For testing spatial interaction, responses to electrical nerve stimulation or mechanical skin stimulation were recorded intracellularly in AC (bandwidth 10 Hz to 10 kHz) before and during radiant heat stimulation of the skin. The responses to electrical stimulation before (control) and during (conditioned) skin stimulation were averaged (8–32 single responses). The control responses and conditioned responses were superimposed and/or the difference was calculated to make the changes more evident (cf. Fig. 1). Responses which were evoked from muscle nerves with a threshold above or around maximal group I stimulus strength (1·5–2·0$T$ for GS, 2·0–2·4$T$ for Q, PBSt and ABSm) and grew with increasing strengths up to about 5$T$ were assumed to be of group II origin, and those occurring with a threshold strength of 7–10$T$ were assumed to be of group III origin (cf. Lundberg, Malmgren & Schomburg, 1987*a*). The incoming volley evoked by electrical nerve stimulation or mechanical skin stimulation was recorded with a unipolar surface electrode from the dorsal root L7 near the entry zone. Generally conditioning stimulation was performed on the ipsilateral side, i.e. the left hindlimb which the motoneurone belonged to. Twenty-seven motoneurones were also tested for conditioning by noxious radiant heat applied to the right hindlimb, which was not denervated.

## RESULTS

### *Basic reflex condition of the preparation*

The effects evoked by electrical stimulation of cutaneous, joint (not tested in all motoneurones) and group II and III muscle afferents coincided with the flexion reflex pattern. The basic reflex condition of our preparation was characterized as follows: (1) in all PBSt motoneurones predominant EPSPs occurred, with notable IPSPs only in four cells; (2) in ABSm motoneurones a mixture of EPSPs and IPSPs (10 cells), predominant EPSPs (11 cells) or predominant IPSPs (4 cells) were observed; (3) in GS motoneurones almost pure IPSPs (14 cells), predominant EPSPs (11 cells) or a mixture of EPSPs and IPSPs (17 cells) were observed; (4) in FDL and Pl motoneurones predominant IPSPs (6 FDL, 6 Pl) were observed, while 2 FDL

motoneurones showed prevalent EPSPs; (5) Tib motoneurones showed predominant EPSPs (3 cells), or a predominant IPSP (1 cell). The mixture of EPSPs and IPSPs consisted partly of combined PSPs with IPSPs following (or overlapping) the EPSPs and partly of a pattern with EPSPs from some nerves and IPSPs from others. The

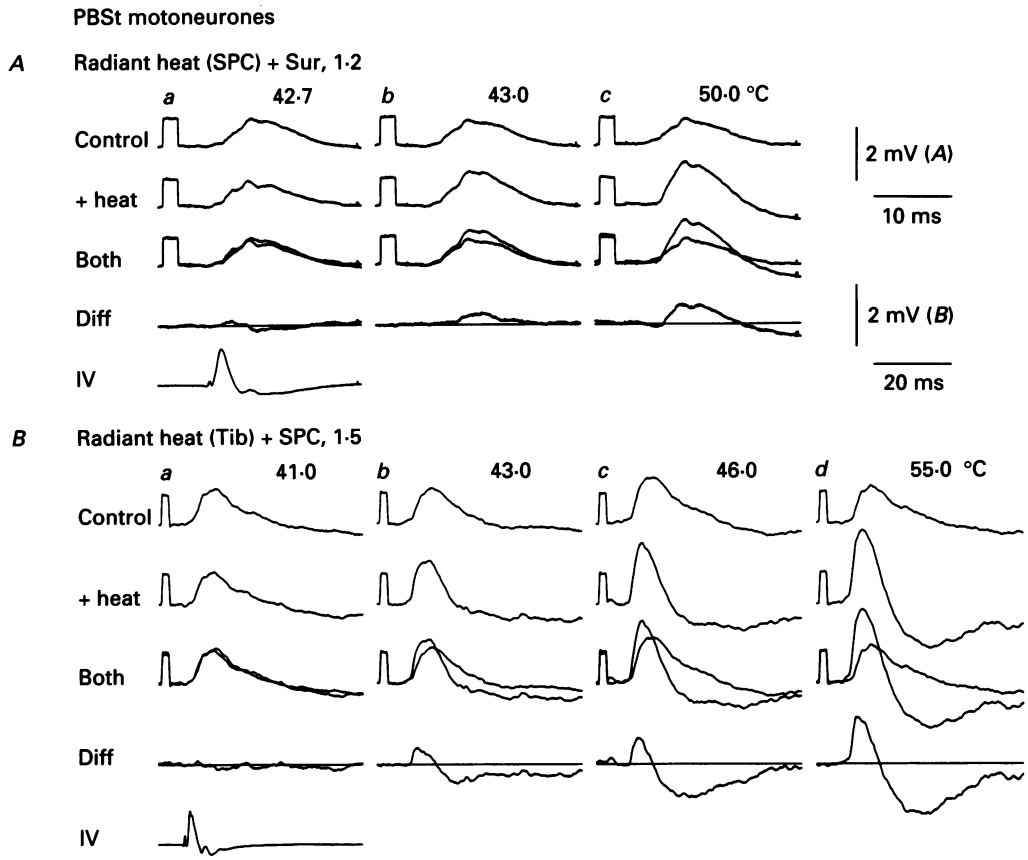


Fig. 1. Threshold of the facilitatory or inhibitory effect of radiant heat. In two PBSt motoneurones (*A* and *B*) the effect of graded radiant heat applied to the areas innervated by SPC (*A*) and Tib (*B*) on the PSPs from Sur with 1·2*T* (*A*) and from SPC with 1·5*T* (*B*) was tested. Control responses on the 1st trace (Control), responses conditioned with heat on the 2nd trace (+heat), control and conditioned response superimposed on the 3rd trace (Both), difference between conditioned and control response on the 4th trace (Diff), and incoming volley from electrical stimulation on the 5th trace (IV). Each record shown is an average of sixteen single responses. Note the different time calibration for *A* and *B*. For all intracellular microelectrode recordings (control, +heat, both) positivity is given in the upward direction. For the incoming volleys positivity is given in the downward direction.

high prevalence of EPSPs in 'ABSm' motoneurones is probably due to the fact that this group may include a fraction of PBSt motoneurones (cf. Methods).

The responses to nociceptive skin stimulation were excitatory in PBSt motoneurones and in ABSm motoneurones that were excited by electrical nerve stimulation. However, for extensor motoneurones (including ABSm motoneurones with mixed or inhibitory input from electrical nerve stimulation) the effects were not

strictly related to the effects of electrical FRA stimulation. Depolarizing effects or increases in synaptic noise without changes of the level of the membrane potential had a higher prevalence than would have been expected from the inhibitory responses to nerve stimulation (cf. Schomburg & Steffens, 1986). The specific nociceptive excitatory non-FRA pathway from the central pad of the foot to plantaris and the intrinsic foot extensors (Schmidt, Schomburg, Steffens, Strohmeyer & Wada, 1987) has been left out of consideration in these investigations.

*Spatial facilitatory action on ipsilateral pathways from cutaneous and joint afferents*

In 90% of the tests ($n > 200$), EPSPs that were evoked in PBSt motoneurones by cutaneous nerve stimulation were facilitated by the conditioning with noxious radiant heat (above 48 °C), provided the stimulus strength was submaximal for cutaneous nerves. The optimum stimulus strength for SPC and Sur was below $1{\cdot}5T$, and for Saph was below $3T$. The higher strength generally needed for Saph stimulation may partly be due to electrode differences, i.e. buried electrode for Saph. Facilitation appeared as an increase in amplitude and/or in the steepness of the rising slope and/or as an earlier onset of the EPSPs (cf. Fig. 1*Bd*).

Facilitation was temperature dependent. The threshold for the facilitatory effect was around 43 °C in most cases (about 70%), lower thresholds (between 41 and 42·5 °C) were more rare (about 10%) than higher ones (above 44·0 °C, about 20%). Differences may be due to individual differences in the cats, e.g. thickness and colour of the skin. With temperatures below 41 °C no reproducible effects could be achieved. As shown in Fig. 1*A*, the threshold could be well defined. In this case radiant heat with a skin temperature of 42·7 °C did not evoke stable effects; a liminal facilitation was sometimes observed. At 43 °C, a stable facilitation occurred which increased with increasing temperature. As stated in the Methods, temperatures above 53°C were not routinely used, but they caused a further increase of the effect.

Facilitation of the responses evoked by cutaneous afferents that had a low threshold to electrical stimulation was also elicited by radiant heat (see Fig. 2). We suggest that this facilitation concerned pathways from afferents of low threshold mechanoreceptors, because reflex actions evoked by afferents from hair follicle receptors and possibly other low threshold mechanoreceptors being activated by an air jet, were also facilitated by noxious radiant heat (Fig. 2*D* and *H*; cf. also Behrends, Schomburg & Steffens, 1983). Spatial facilitation was also observed in cases with higher electrical stimulation strength (up to $5T$) provided the response to the unconditioned stimulus was small (cf. Fig. 2*A*). The amount of facilitation by conditioning radiant heat could vary considerably from cell to cell and from one cutaneous nerve to the other. With small unconditioned responses below 1 mV the facilitation could reach 2·3 mV. On the whole, in two-thirds of positive tests the facilitation had a range up to 1 mV and in one-third more than 1 mV. If the amplitude of the unconditioned response itself was large (exceeding several millivolts, a fixed critical value could not be determined) the facilitation by conditioning radiant heat was distinctly smaller or even absent. As far as could be determined with the technique used, there was no systematic local specificity for the occurrence of spatial facilitation. As shown in Fig. 2*E–H* EPSPs evoked by Saph, SPC and lSur stimulation or by a mechanosensitive input from mSur were all facilitated by

nociceptive afferents from the area innervated by the mSur nerve. In this case the facilitation of the response to SPC was maximum but this was not a systematic finding. Control tests with a radiant heat temperature of 43 °C proved that this effect did not originate from thermoreceptive afferents (Fig. 2*A–D*). Correspondingly,

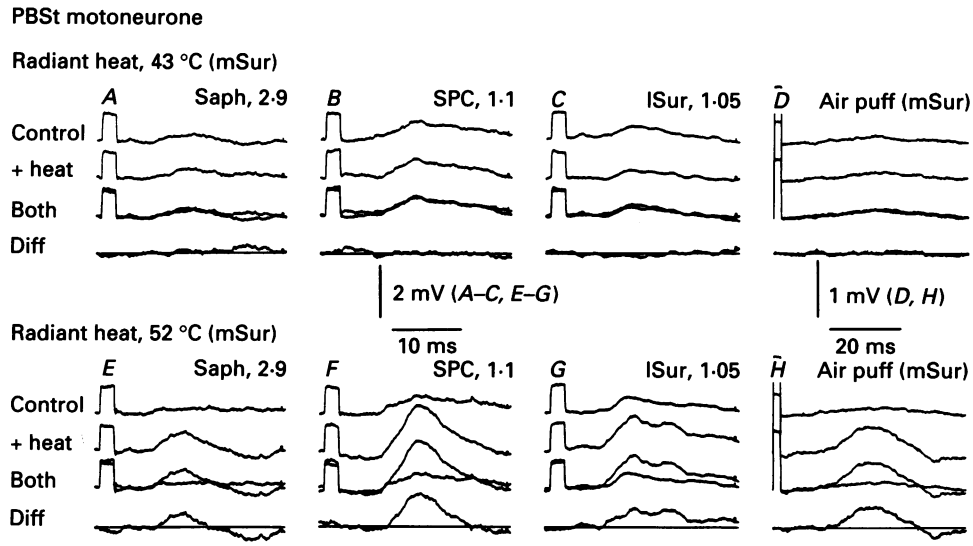


Fig. 2. Facilitation of excitatory reflex pathways from various electrically (*A–C* and *E–G*) and mechanically activated (*D* and *H*) cutaneous afferents by nociceptive afferents. Intracellular recordings of a PBSt motoneurone; electrical stimulation of Saph with 2·9*T* (*A* and *E*), SPC with 1·1*T* (*B* and *F*), lSur with 1·05*T* (*C* and *G*), and activation of mechanosensitive afferents by an air puff applied to the area innervated by mSur (*D* and *H*). Radiant heat (43 °C, in *A–D*; 52 °C, in *E–H*) was applied to the area innervated by mSur. Traces 1–4 as in Fig. 1. Each record shown is an average of sixteen (*A–C*, *E–G*) or thirty-two (*D* and *H*) single responses.

facilitatory conditioning effects could be elicited by noxious radiant heat stimuli applied to different hindlimb areas innervated by the mSur, SPC, Saph or Tib nerve.

Excitation evoked in PBSt motoneurones by knee joint nerve stimulation (1·5–3*T*) was facilitated by a nociceptive cutaneous input from the areas innervated by SPC and mSur (Tib not tested for technical reasons) in the same way as the excitation from cutaneous nerve stimulation.

Testing spatial facilitation in inhibitory pathways has to be regarded with some precaution and limitation, since facilitation may be absent but simulated by the influence of a membrane depolarization or it may be present but hidden behind a depression of the IPSP due to a membrane hyperpolarization (for further details see Discussion). In consideration of these facts we tested spatial facilitation of IPSPs only in extensor motoneurones which did not show any significant change of the level of the membrane potential (cf. Fig. 4) during activation of the nociceptive input, or which were hyperpolarized by this input. Figure 3 shows that even in the latter case IPSPs evoked by low threshold cutaneous afferents (SPC in *A–C*, lSur in *D–F*) could be distinctly facilitated by application of noxious radiant heat. The facilitation is evident from the slightly earlier and steeper onset of the IPSPs and an increase of

their amplitude. Considering the hyperpolarization induced by the nociceptive input, this increase of the amplitude may be assumed not to represent the real amount of facilitation.

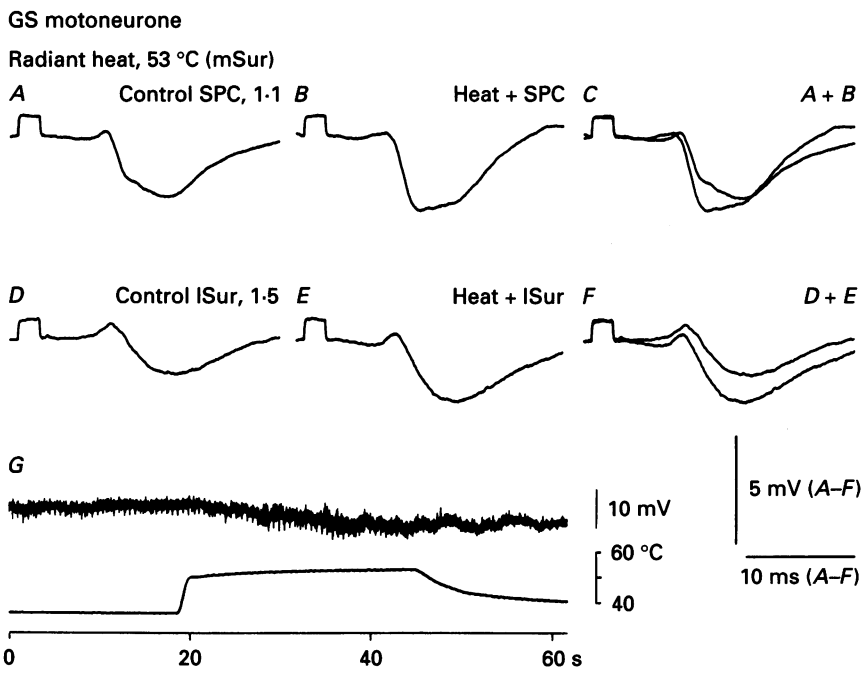


Fig. 3. Facilitation of IPSPs in an extensor motoneurone which was hyperpolarized during the conditioning application of radiant heat (area innervated by mSur). Intracellular recordings of a GS motoneurone; electrical stimulation of SPC with 1·1*T* (*A–C*) and of lSur with 1·5*T* (*D–F*). *G*, DC recording of the membrane potential and temperature course during application of radiant heat. *A* and *D*, control responses; *B* and *E*, responses conditioned with radiant heat; *C* and *F*, control responses and conditioned responses superimposed. Records in *A–F* are averages of sixteen responses each.

Recording of the extracellular fields proved that the spatial facilitation of IPSPs by the nociceptive input was not substantially influenced by these fields. Figure 4 includes examples of spatial facilitation of IPSPs evoked by group II muscle afferents (*A*), joint afferents (*B*) and cutaneous afferents (*C* and *D*). If so, there were only very small changes in the extracellular field potential (traces 5 and 6) during application of radiant heat, proving that these fields do not contribute to the intracellularly recorded facilitatory effects.

In spinal cats responses of motoneurones, particularly of extensor motoneurones, may consist of a combination of EPSPs and IPSPs. The IPSPs may be more or less covered by the EPSPs (Schomburg & Steffens, 1986). It was demonstrated that in PBSt motoneurones (5 cases) the spatial facilitation of such IPSPs from cutaneous afferents was always accompanied by facilitation of the preceding EPSP, both having the same threshold for the conditioning temperature (Fig. 1*Ba–d*). In extensor motoneurones, even those with a predominant EPSP from cutaneous afferents, generally only the IPSP was facilitated. This could result in a mere

reduction of the amplitude of EPSP; but as shown in Fig. 5*A* the facilitation of the amplitude of the IPSP could be accompanied by a reduction of the latency of the IPSP. The spatial facilitation of IPSPs also applied to responses to stimulation of the cutaneous afferents with higher threshold and when no IPSP would have been

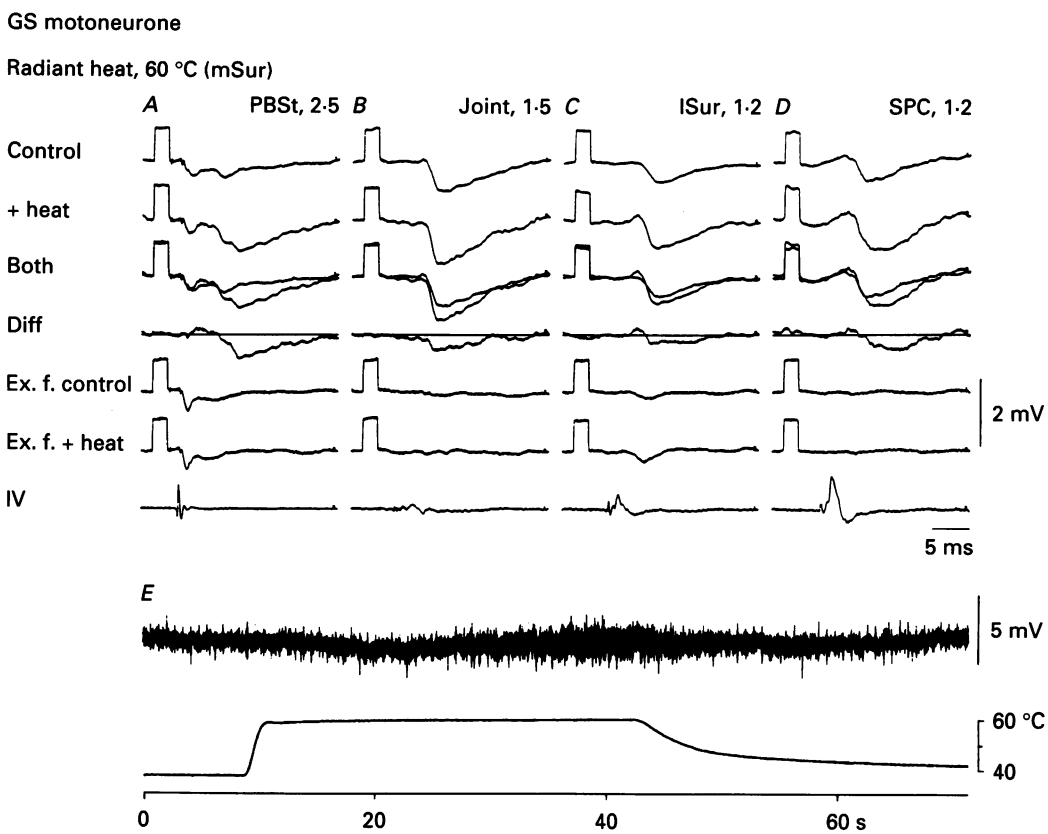


Fig. 4. Facilitation of IPSPs in an extensor motoneurone without corresponding changes of extracellular field potentials. Recordings of a GS motoneurone; electrical stimulation of PBSt (2·5*T*, *A*), joint (1·5*T*, *B*), lSur (1·2*T*, *C*) and SPC (1·2*T*, *D*). Traces 1–4 as in Fig. 1, traces 5 and 6 extracellular field potential; 5th trace (Ex. f. control) controls, 6th trace (Ex. f. +heat) conditioned with radiant heat, 7th trace (IV) incoming volley from electrical nerve stimulation. Radiant heat (60 °C) was applied to the area innervated by mSur. Records *A–D* are averages of sixteen single responses each. *E*, DC recording of the membrane potential and temperature course during application of radiant heat.

expected in the response (3*T* in Fig. 5*C*). The time course of the facilitation of the IPSP which is evident as a depression of the EPSP is shown in Fig. 5*D*. From Fig. 5*D*, *E* and *F* it is evident that this depression of the EPSP – or the facilitation of the IPSP – was not related to changes of the level of the membrane potential. It was already at its maximum (in *E*) before the depolarization of the membrane potential occurred (in *F*).

The late depression which was observed after facilitatory effects (Figs 1*A c* and 2*E*) could not be reversed by hyperpolarizing current and chloride injection and has to be regarded as a disfacilitation.

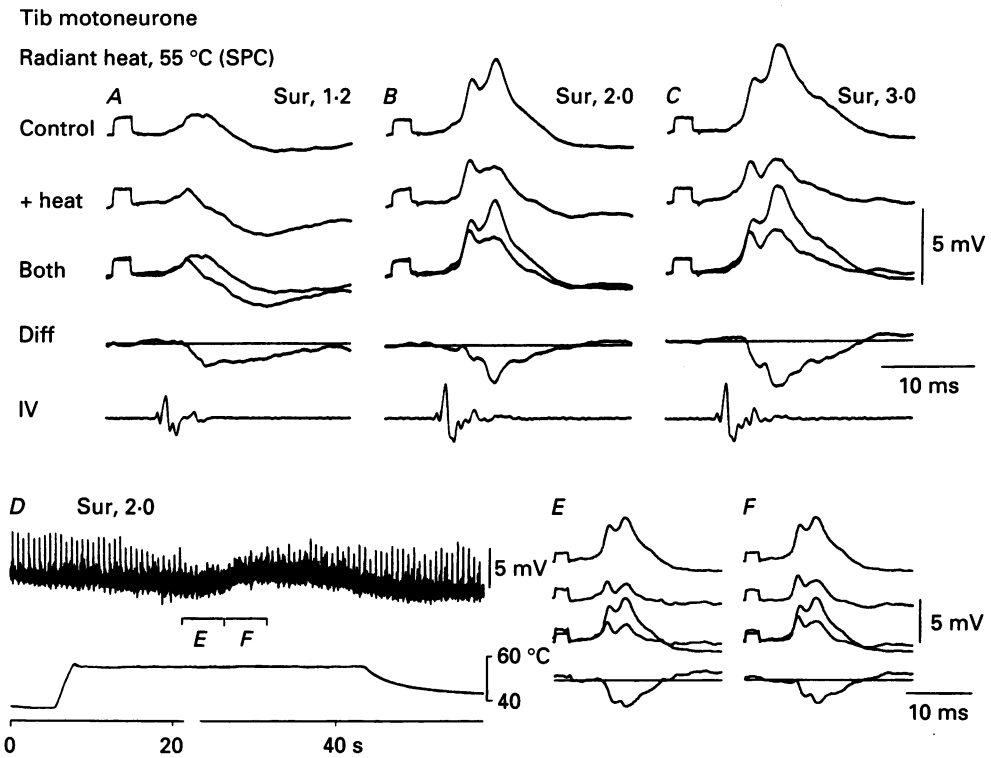


Fig. 5. Facilitation of a 'hidden' IPSP by application of radiant heat (55 °C to the area innervated by SPC). Recordings of a Tib motoneurone, electrical stimulation of Sur with 1·2*T* (*A*), 2·0*T* (*B*) and 3·0*T* (*C*). Traces 1–4 as in Fig. 1, 5th trace (IV) incoming volley from electrical stimulation. Records in *A–C* are averages of sixteen single responses each. *D*, DC recording of the membrane potential and temperature course during radiant heat application. Records in *E* and *F* represent averages (8 responses each) taken from the corresponding sections marked in *D*.

*Spatial facilitation of ipsilateral pathways from muscle afferents*

Monosynaptic Ia EPSPs were never facilitated but in one-quarter of cases diminished (reduction up to 27%) by the nociceptive input.

Despite the well-known wide convergence from FRA on Ia inhibitory interneurones (Hultborn, Illert & Santini, 1976) it was difficult to obtain facilitation from nociceptive afferents to the reciprocal group Ia inhibitory pathway. A weak facilitation occurred in only two cases. Figure 6*A a* shows that even a small reciprocal group Ia IPSP evoked in a PBSt motoneurone by just suprathreshold stimulation of the Q nerve was not facilitated by noxious radiant heat. The successful facilitation of the heteronymous oligosynaptic group I (in *A d* and *A e*) and group II EPSPs (*A c*) by noxious radiant heat (cf. below) demonstrated that the failure of facilitation of group Ia inhibition cannot be attributed to an ineffective noxious input.

Oligosynaptic group I (group Ib with possible group Ia contribution, cf. Jankowska & McCrea, 1983) excitation was facilitated by conditioning with noxious radiant heat, but the amount of facilitation was generally small and did not exceed 1·2 mV. Figure 6 shows that with a stimulus strength well below group II threshold

(1·3–1·4$T$ in Fig. 6$Ad$ and $Ba$ and $b$) no distinct excitation was evoked, but conditioning with radiant heat facilitated a response EPSP. The facilitation increased further when group II threshold (1·6$T$ in Fig 6$Ae$) was reached or exceeded (2·5$T$ in Fig. 6$Af$). The latency of the facilitated group I EPSPs to the group I incoming volley ranged from 1·3–3·2 ms.

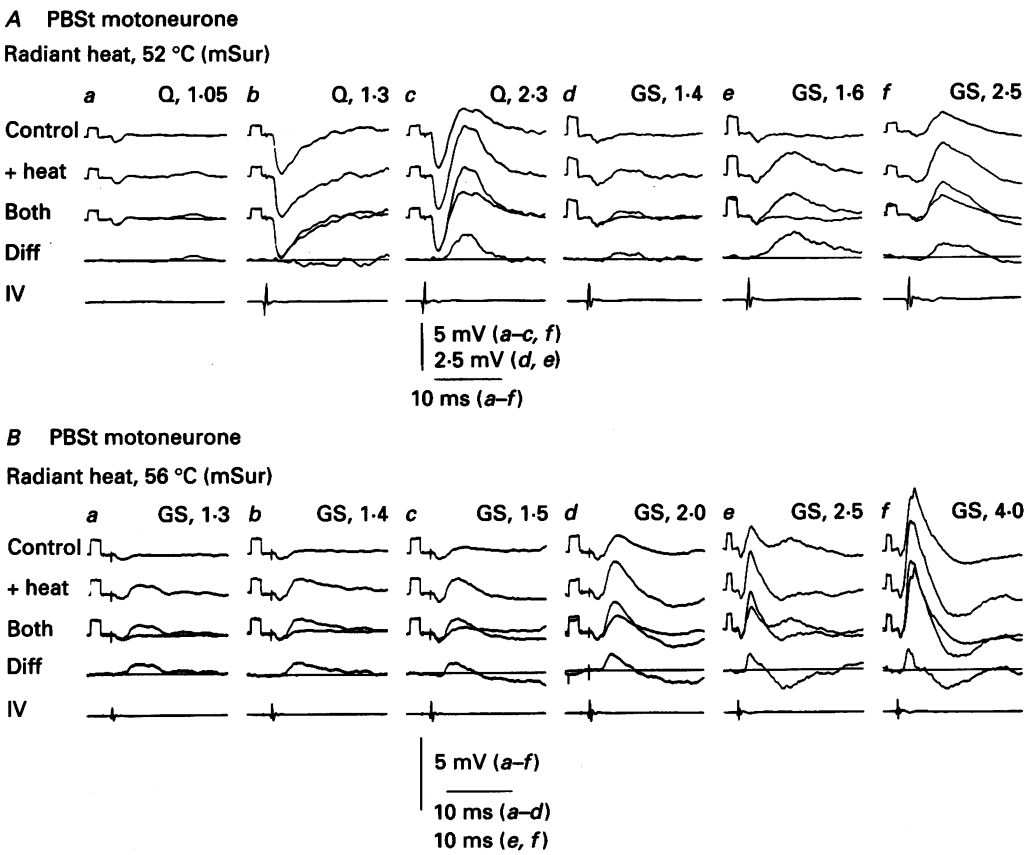


Fig. 6. Facilitation of group Ib EPSPs ($Ad$–$e$, $Ba$–$c$) and heteronymous group II EPSPs ($Ae$ and $f$) and IPSPs ($Bc$–$f$) by nociceptive afferents, and failure of facilitation of the reciprocal group Ia IPSP ($Aa$–$c$). In two PBSt motoneurones ($A$ and $B$) the effect of radiant heat application ($A$, 52 °C; $B$, 56 °C; both in the area innervated by mSur) was tested on group I and II effects evoked by graded electrical muscle nerve stimulation: Q with 1·05–2·3$T$ ($Aa$–$c$), GS with 1·4–2·5$T$ ($Ad$–$f$), GS with 1·3–4·0$T$ ($Ba$–$f$). Traces 1–5 as in Fig. 5. All records are averages of sixteen responses each. Different calibration for $A$ and $B$.

Like monosynaptic Ia EPSPs monosynaptic group II EPSPs were never facilitated but depressed by the conditioning nociceptive input (Kirkwood, Schomburg & Steffens, 1987).

EPSPs evoked by group II muscle afferents were facilitated more (up to 2·5 mV) than oligosynaptic group Ib EPSPs by nociceptive cutaneous afferents. This facilitation occurred in effects from homonymous group II muscle afferents as well as in those from heteronymous synergistic and antagonistic muscles.

Figure 6 shows the facilitatory influence of nociceptive afferents on a group II response from antagonistic muscle afferents in PBSt motoneurones. In the neurone shown in Fig. 6*A* a small EPSP occurred when the stimulus strength of the Q nerve stimulation was raised above group II threshold (from 1·3 in *b*, to 2·3*T* in *c*). This EPSP was clearly facilitated by the conditioning stimulation of nociceptive afferents.

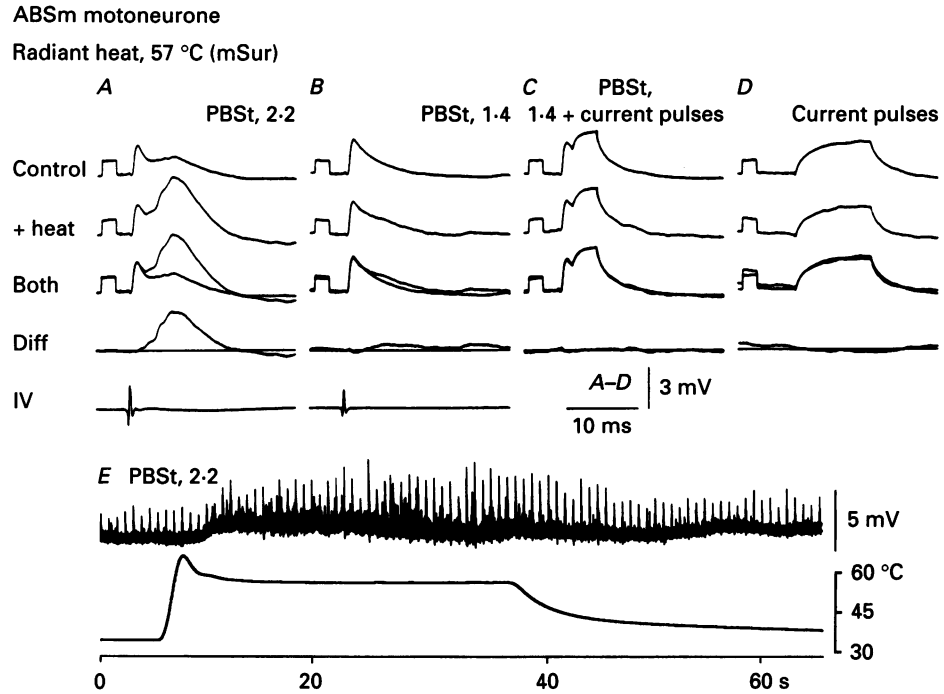


Fig. 7. Facilitation of di- and oligosynaptic group II EPSPs (*A–E*) by nociceptive afferents. Exclusion of a causative influence of changes at the motoneuronal membrane: no alteration of the monosynaptic group I EPSP (*A* and *B*), no alteration of the response to depolarizing current pulses (*C* and *D*). Intracellular recordings of an ABSm motoneurone. Electrical stimulation of the PBSt nerve with 2·2*T* (*A*, low group II range) and 1·4*T* (*B* and *C*, group Ia range). Nociceptive afferents activated by noxious heat (57 °C) applied in the area innervated by mSur. Current pulses applied at the declining slope of a monosynaptic group Ia EPSP (*C*, location like the group II EPSP) and at the basic membrane potential (*D*). The records in *A–D* were averaged from sixteen single responses each. Traces in *A–D* as in Fig. 5*A–C* and in *E* as in Fig. 5*D*.

As observed with excitatory cutaneous responses, a conditioning nociceptive input could facilitate an inhibitory effect from group II muscle afferents to a PBSt motoneurone despite an excitatory unconditioned basic effect of these afferents (Fig. 6*B*). When exceeding the threshold for group II afferents for stimulation at the GS nerve (1·5*T* in *c*) the facilitated excitatory group I EPSP was followed by an inhibition during conditioning nociceptive stimulation. An increase of the stimulus strength at the GS nerve well above group II threshold (2·5*T* in *e*) evoked a late EPSP, which was turned to an inhibition during the nociceptive input. After further increase of the stimulus strength the unconditioned stimulus by itself caused an

inhibition which was facilitated by the nociceptive input. Such an uncovering of inhibitory effects from group II muscle afferents to a flexor by nociceptive input was only observed in four PBSt motoneurones, but proved to be very stable.

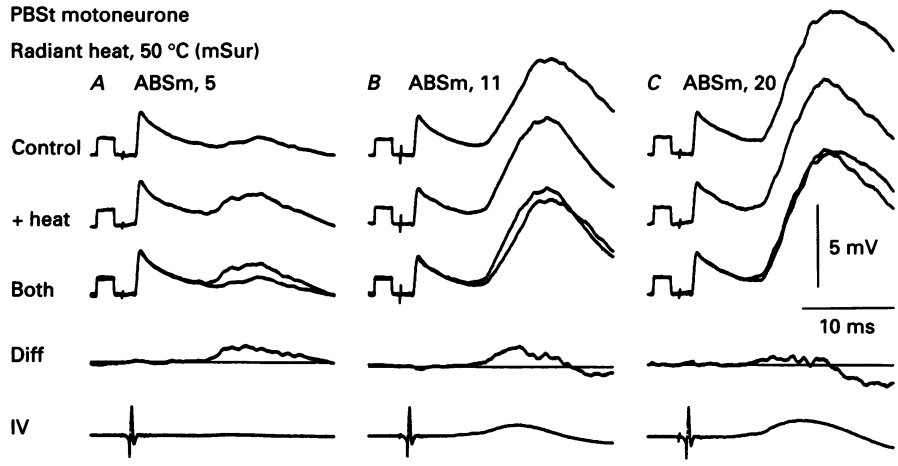


Fig. 8. Nociceptive afferents facilitate a polysynaptic longer latency group II EPSP (*A* and *B*) in a PBSt motoneurone. Late inhibition when stimulus strength exceeded group III threshold (*B* and *C*). Stimulation of ABSm with 5 (*A*), 11 (*B*) and 20*T* (*C*). Radiant heat (50 °C) was applied to the receptive field of mSur. Traces as in Fig. 1. The records were averaged from sixteen single responses each.

Spatial facilitation of group II EPSPs in closely related synergists is shown in Fig. 7. A small EPSP evoked in an ABSm motoneurone by stimulation of the PBSt nerve in the low group II range (2·2*T* in *A*) was distinctly facilitated by noxious radiant heat applied to the skin area innervated by the mSur. Stimulation with a strength below group II threshold (1·4*T* in *B*) did not produce any consistent effect. Figure 7 gives several indications that the changes induced by the nociceptive input are not due to changes at the motoneuronal membrane but rather at the premotoneuronal level: (1) the monosynaptic Ia EPSP is not changed at all; (2) the maximal facilitation of the group II EPSPs did not occur during maximal membrane depolarization but rather when the membrane potential was declining again (see directly recorded responses in *E*); (3) current pulses applied to the declining slope of the monosynaptic Ia EPSP (in *C*) or without any stimulation to the basic membrane potential (in *D*) were not changed by conditioning with noxious radiant heat.

Spatial facilitatory effects were observed on both short latency disynaptic and oligosynaptic group II EPSPs (2·4–4 ms latency to group I incoming volley; Figs 6 and 7) and longer latency EPSPs (Fig. 8). The group II EPSP which occurred with a latency of 9 ms to group I incoming volley, was evoked by stimulation of the ABSm nerve. It was constantly facilitated by conditioning stimulation with noxious radiant heat. This effect cannot be attributed to a group III response since it developed well below group III threshold (Fig. 8*A*). Moreover, the later occurring group III responses were inhibited by the nociceptive input (Fig. 8*B* and *C*).

In extensor motoneurones PSPs evoked by homonymous and heteronymous group II and group III muscle afferents were not influenced in a uniform way by

conditioning stimulation with noxious radiant heat. IPSPs evoked by these afferents were generally facilitated (for group II IPSP see Fig. 4*A*, for group III IPSP see Fig. 9*A e* and *B e*). However, one has to keep in mind the above stated precautions for IPSPs. EPSPs could be either facilitated or inhibited. In Fig. 9*A a–d* the

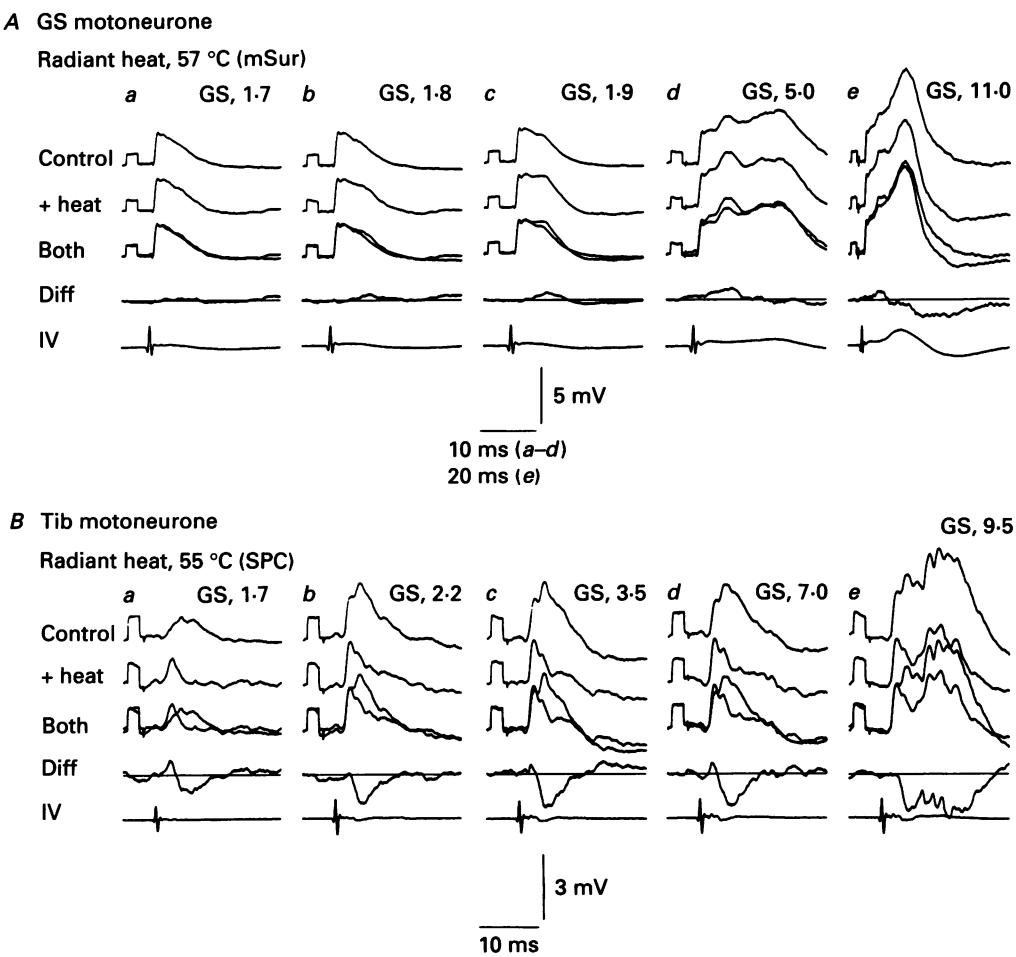


Fig. 9. Influence of conditioning radiant heat on group II and III PSPs from homonymous and heteronymous muscle nerves in extensor motoneurones. *A*, intracellular recordings of a GS motoneurone, graded electrical stimulation of GS with 1·7–11*T*; *B*, intracellular recording responses of a Tib motoneurone, graded electrical stimulation of GS with 1·7–9·5*T*. Facilitation of group II EPSP (*A a–d*) and of group III IPSP (*A e*) from the homonymous muscle nerve. Inhibition of group II and III EPSPs (*B a–e*) from the heteronymous muscle nerve. Conditioning radiant heat was applied to the receptive field of mSur (57 °C, *A*) and SPC (55 °C, *B*). Traces as in Fig. 1. Records were averaged from sixteen single responses each. Note the different time calibration in *A e*.

homonymous group II EPSP was clearly facilitated by the conditioning nociceptive input (the later group III IPSP, in *A e* was also facilitated). On the other hand the heteronymous group II EPSP occurring in the Tib motoneurone shown in Fig.

9*Ba–d*) was distinctly inhibited or a superimposed IPSP was facilitated by the nociceptive input. The EPSP which was additionally evoked when the stimulus strength exceeded group III threshold (9·5*T* in *A e*) was influenced in the same way as the group II EPSP.

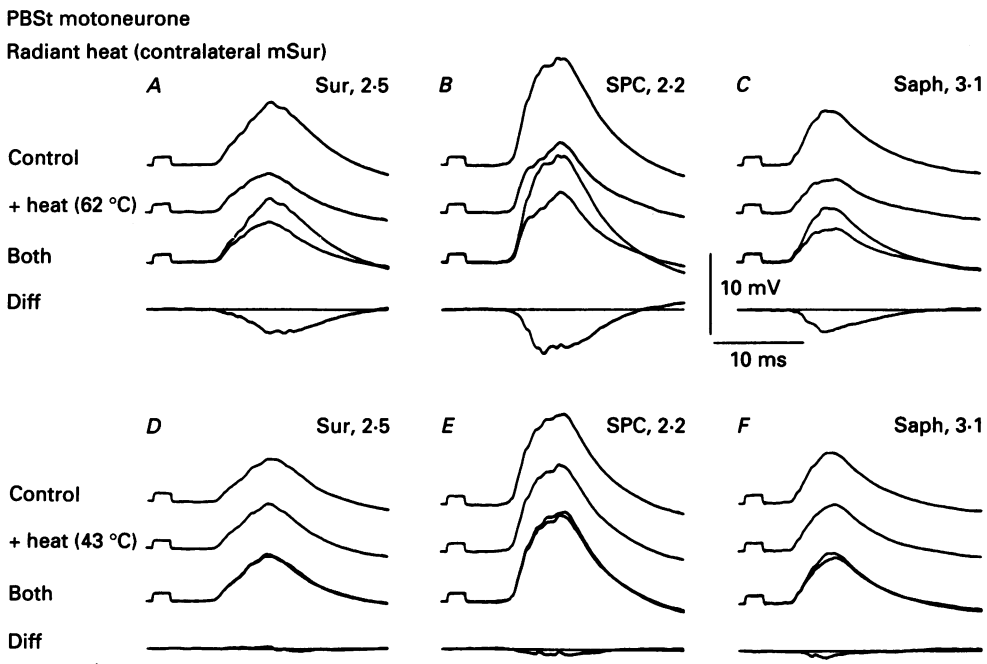


Fig. 10. Inhibitory influence of contralaterally activated nociceptive afferents on EPSPs evoked by electrical cutaneous stimulation in a PBSt motoneurone. Electrical stimulation of Sur with 2·5*T* (*A* and *D*), of SPC with 2·2*T* (*B* and *E*) and of Saph with 3·1*T* (*C* and *F*). Radiant heat (62 °C in *A–C*, 43 °C in *D–E*) applied to the area innervated by the contralateral mSur. Traces as in Fig. 2. All records were averaged from sixteen single responses each.

*Spatial interaction of nociceptive afferents on contralateral segmental pathways*

Contralateral application of radiant heat evoked a less consistent response on the motoneuronal membrane potentials than ipsilateral stimulation. In twenty of the cells which were tested ($n = 27$), no systematic change of the membrane potential occurred. Five of these twenty cells showed a slight increase of synaptic noise. The other seven cells showed a marked increase of the synaptic noise and, in the case of all four PBSt motoneurones, were additionally hyperpolarized (up to 1 mV) during application of radiant heat to the contralateral hindlimb.

Spatial conditioning effects of contralateral application of noxious radiant heat were smaller than those of ipsilateral application or they were even missing. Therefore, the investigations on the crossing spatial effects from nociceptive afferents had to be performed with higher temperatures (up to 65 °C) in order to get clear effects. This caused some restrictions of the systematic investigation, since frequent application of these temperatures was not possible (cf. Methods).

Figure 10 shows the influence of contralaterally applied noxious heat (area of the mSur) on EPSP evoked in a PBSt motoneurone by cutaneous nerve stimulation. No effects were observed as long as the temperature of radiant heat was kept below 43 °C. At 43 °C a threshold effect was evident (*D–F*) and with higher temperatures

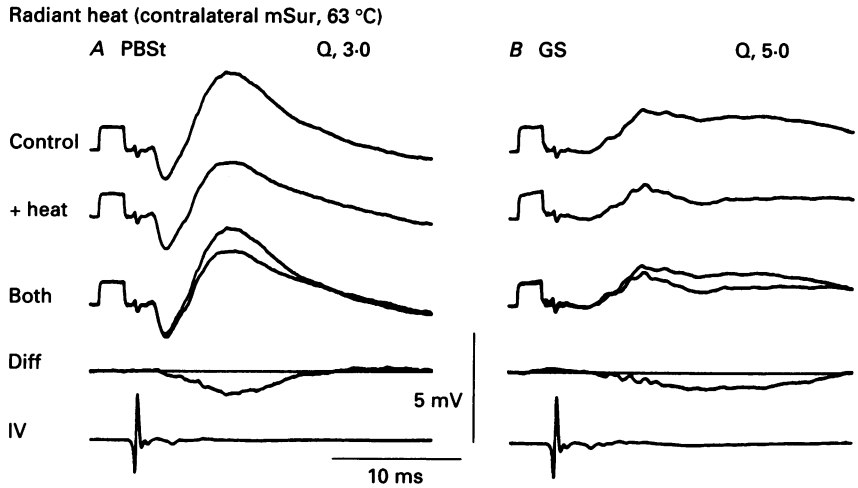


Fig. 11. Inhibitory influence of contralaterally activated nociceptive afferents on group II EPSPs in a flexor (*A*, PBSt) and an extensor (*B*, GS) motoneurone. Electrical stimulation of Q with 3·0*T* (*A*) and 5·0*T* (*B*). Radiant heat was applied to the contralateral receptive field of mSur (63 °C). Reciprocal group Ia inhibition was not affected by radiant heat (*A*). Traces as in Fig. 1. All records were averaged from sixteen single responses each.

(62 °C), a depression of the EPSPs occurred. Again, as with ipsilateral application, contralateral nociceptive stimulation of the foot did not show a systematic local specificity. The EPSPs were inhibited, no matter which cutaneous nerve was stimulated electrically.

EPSPs evoked by group II muscle afferents in flexor or extensor motoneurones were also inhibited by contralateral nociceptive afferents. In Fig. 11 stimulation of Q group II afferents caused an EPSP in a PBSt and in a GS motoneurone (control). In both cases the EPSP was depressed by conditioning contralateral radiant heat. The reciprocal Ia IPSPs from Q in PBSt motoneurones did not show any systematic change during contralateral nociceptive conditioning.

## DISCUSSION

The investigations revealed a facilitatory interaction of the pathways from afferents activated by noxious radiant heat with ipsilateral segmental reflex pathways from FRA, i.e. group II and III muscle afferents, low to medium threshold cutaneous afferents and joint afferents, and from group Ib muscle afferents. The observed spatial facilitatory effects caused by the radiant heat cannot derive from warm receptor activation since they occurred only if stimulation temperatures were

well above pain threshold and since they could be graded above this threshold (cf. also Schomburg & Steffens, 1986). Thus, they fulfil the two conditions for nociceptor activation: (1) a defined threshold condition and (2) an intensity encoding above threshold condition (Besson & Chaouch, 1987; cf. also Willis, 1985). However, it has to be taken into account that mechanoreceptive A$\delta$ fibres may be sensitized by repetitive thermal stimulation within the range of 50–55 °C (Fitzgerald & Lynn, 1977). A substantial contribution by sensitized mechanoreceptors to the results may be excluded for the following reasons. The threshold and the intensity–effect relation of the heat stimulation did not show corresponding changes. If the responsiveness was changing in the course of the experiment, it was decreasing but not increasing. The effects could also be observed in a stable manner in experiments in which the stimulus temperature was kept below 50 °C throughout the experiment. It is noteworthy that the results confirm the assumption that warm receptors do not effectively evoke segmental motor actions, at least under the given experimental conditions (cf. Schomburg, 1990).

*Convergent afferent input on common interneurones*

The technique of testing for spatial facilitation has been successfully used for a long time to investigate convergence onto common interneurones in segment reflex pathways (for reviews see Lundberg, 1975; Baldissera *et al.* 1981; Jankowska & Lundberg, 1981; Schomburg, 1990). However, in any case the results of testing for spatial facilitation require some consideration before a conclusion on the existence or absence of convergence may be drawn. Spatial interaction may generally take place at the interneuronal, as well as at the motoneuronal level or at a presynaptic level at the terminals of the primary afferents. The latter possibility particularly has to be excluded in cases with a long-lasting conditioning input as in the present experiments.

A causative influence of membrane changes on the observed facilitation of EPSPs by the nociceptive input can be excluded for several reasons: (1) owing to the linear current–voltage relation around the resting potential of motoneurones for small EPSPs (as used in the presented data) an almost algebraic summation can be assumed (cf. Discussion by Schomburg, Steffens & Warneke, 1986 and by Lundberg, Malmgren & Schomburg, 1987*b*); (2) membrane responses to current pulses given under comparable conditions did not show any changes (cf. Fig. 7); (3) in many cases maximal spatial facilitation did not coincide with the phase of maximal membrane depolarization (cf. Fig. 7); (4) monosynaptic group Ia EPSPs did not show any spatial facilitation even if concomitant group II EPSPs were distinctly enhanced (cf. Figs 7–9).

Owing to the vicinity of the motoneuronal resting potential to the equilibrium potential of IPSPs changes of the motoneuronal membrane potential may cause distinct changes in their amplitude. Therefore, an increase of an IPSP by conditioning radiant heat was only accepted as positive spatial facilitation, if the membrane potential was unchanged or the membrane was hyperpolarized by the nociceptive input (cf. Figs 3 and 4), even if it could be demonstrated that small depolarization did not have an important influence (cf. Fig. 5).

Changing extracellular fields may cause a further falsifying influence upon the amplitude of conditioned IPSPs. However, these fields which were recorded in direct

vicinity to the recorded motoneurones never showed a comparable change of their amplitude during the nociceptive input.

Primary afferent depolarization (PAD) as a reason for the observed spatial facilitation of group Ib PSPs and synaptic responses from flexor reflex afferents by the nociceptive input is also highly improbable. PAD of group Ib and flexor reflex afferents by activation of nociceptive cutaneous afferents has indeed been demonstrated (Burke, Rudomin, Vyklicky & Zajac, 1971; Jänig & Zimmermann, 1971; Whitehorn & Burgess, 1973). However, this would cause an inhibition rather than a facilitation of the synaptic responses by nociceptive conditioning. The fact that monosynaptic group Ia EPSPs were reduced by a nociceptive input in about one-quarter of tested cases confirms the results of Burke *et al.* (1971) who stated that there is 'evidence that PAD (from nociceptive afferents) may occur in group Ia afferents as well'. This would contradict the assumption that FRAs do not evoke PADs in group Ia terminals in the 'normal ' spinal cat (Eccles, Magni & Willis, 1962) and that this pathway is only released by activation of the noradrenergic reticulospinal pathways with L-3,4-dihydroxyphenylalanine (L-DOPA; Andén, Jukes, Lundberg & Vyklicky, 1966; cf. also Baldissera *et al.* 1981). All in all we presume that the observed spatial facilitation was caused by a convergence of nociceptive afferents and the corresponding tested afferents onto common interneurones in the segmental pathways to $\alpha$-motoneurones.

The missing or only liminal spatial facilitation of reciprocal Ia inhibition by nociceptive afferents was surprising, since distinct influences from FRA onto the Ia-inhibitory pathway have been described (Fedina & Hultborn, 1972; Hultborn, 1972, 1976). The missing facilitatory effect of cutaneous afferents with a stimulus strength of more than 3 times threshold observed in those experiments was explained by occlusion (Hultborn, 1972). However, it has to be considered that a convergence from nociceptive cutaneous afferents on the Ia reciprocal pathway may be missing. At least it can be concluded that facilitation of FRA-derived IPSPs by noxious radiant heat was probably due to a facilitation of inhibitory pathways not being mediated via the Ia-inhibitory interneurone.

The latencies of the EPSPs and IPSPs facilitated showed that di- and trisynaptic as well as polysynaptic connections from group Ib (possibly with Ia contribution, Harrison & Jankowska, 1985) and group II afferents to $\alpha$-motoneurones get a convergent input from nociceptive afferents (cf. also Eccles, Eccles & Lundberg, 1957; Malmgren & Schomburg, 1977, 1987*a*, *b*). In group II pathways particularly it became evident that the disynaptic pathway often showed just a liminal transmission without conditioning stimulation but could be facilitated by the nociceptive input very effectively (cf. Fig. 7). On the other hand the long latency polysynaptic group II pathways could be facilitated independently from the oligosynaptic pathways (cf. Fig. 8). This confirms the assumption that even at the segmental level there may be an independent control of the transmission in the different group II pathways (cf. Lundberg *et al.* 1987*c*).

It cannot be excluded that free nerve endings have partly contributed to the group II responses facilitated by the nociceptive input. However, facilitation generally occurred best with a stimulus strength in the low group II range. A contribution of free nerve endings which has mainly to be expected in the high group II range (for

more detailed discussions see Lundberg *et al.* 1987*a*; Schomburg, 1990) therefore seems quite improbable. We therefore assume that at least a large part of the observed facilitation of group II responses by the nociceptive input can be attributed to secondary spindle afferents. This assumption is supported by experiments with spike-triggered averaging which showed a facilitation of synaptic effects of identified secondary spindle afferents by a conditioning nociceptive input (Kirkwood *et al.* 1987).

The inhibitory effects of nociceptive afferent activity on FRA-evoked EPSPs in some $\alpha$-motoneurones suggest that there were inhibitory FRA pathways being activated in parallel to the excitatory ones (cf. Schomburg & Steffens, 1986). These inhibitory pathways then have to be assumed to be more effectively facilitated by the nociceptive input than the excitatory pathways.

The crossed effects from contralaterally activated nociceptive afferents on ipsilateral motoneurones are in line with the typical crossed effects from flexor reflex afferents (Holmqvist, 1961). However, at least under the given experimental conditions this pathway from nociceptive afferents seems to be quite weak and needs spatial facilitation to become effective. The crossing effect is possibly mediated via lamina VIII interneurones which have been shown to receive a wide FRA input, particularly from higher threshold muscle and cutaneous afferents (Grillner & Hongo, 1972; Harrison, Jankowska & Zytnicki, 1986).

*Segmental motor functions of nociceptive cutaneous afferents in connection with the FRA*

In order to avoid misunderstandings it is important to realize that a large fraction of afferents grouped together as FRAs can be activated by receptors being excited during normal movements (Lundberg, 1979; Lundberg *et al.* 1987*c*). The FRA hypothesis proposed by Lundberg suggests that the interneurones of the segmental FRA pathways are used to mediate descending commands from the brain for the activation of motoneurones and the performance of movements. The afferent multisensorial activity being evoked by the on-going movement in muscle, skin and joint receptors is channelled back to the interneurones of the FRA pathway which are already activated by the descending command. The specificity of a more or less complex movement may be accomplished by the selection of an appropriate subgroup of interneurones in the different available FRA pathways. According to the hypothesis inhibitory interactive connections between the FRA pathways suppress transmission in those pathways not being used by the descending command (Lundberg, 1969, 1975, 1979; Lundberg *et al.* 1987*c*). Thereby it is assured that the utilized interneuronal pathway is positively reinforced, in spite of the diffuse unspecific multisensory feedback from a wide receptive field.

The original hypothesis was mainly based on the assumption of a mechanosensitive feedback occurring during 'normal' movements. However, the wide convergence from nociceptive afferents onto the interneurones of the FRA pathways suggest that these afferents may substantially contribute to the FRA system. Thus they add a more specific component to this generally unspecific system with respect to nocifension. But it has to be stressed particularly that nocifension is not supposed to be the main basic function of the FRA systems. The advantage of the wide multisensorial and descending convergence observed in the FRA pathways was

thought of as a possibility to keep the reflex gain in the different pathways low at rest. Passive movements and manipulations would therefore not evoke reflexes (Lundberg *et al.* 1987*c*). For nocifension the function of spatial facilitation which is achieved by the afferent convergence onto common interneurones is also evident. A protective motor reaction to a nociceptive input will be accelerated and enhanced by a concomitant activation by other FRA, e.g. a nocifensive reaction to a strong mechanical stimulus will be facilitated by the concomitant activation of mechanosensitive afferents. If on the other hand a movement reaches a noxious stage for a joint the braking of this movement will be facilitated by the spatial interaction of activated joint and nociceptive afferents (Behrends *et al.* 1983; Schomburg, 1988, 1991; cf. also Lundberg, Malmgren & Schomburg, 1978). Thus, the spatial facilitation of nociceptive pathways by FRA and group Ib afferents may facilitate corrections of a movement as soon as it reaches a hurtful stage.

The publication presents part of the results of the Habilitation Thesis of H. Steffens. The work was supported by the Deutsche Forschungsgemeinschaft (Scho 37/3-2,3).

## REFERENCES

ANDÉN, N.-E., JUKES, M. G. M., LUNDBERG, A. & VYKLICKY, L. (1966). The effect of DOPA on the spinal cord. 3. Depolarization evoked in the central terminals of ipsilateral Ia afferents by volleys in the flexor reflex afferents. *Acta Physiologica Scandinavica* **68**, 322–336.

BALDISSERA, F., HULTBORN, H. & ILLERT, M. (1981). Integration in spinal neuronal systems. In *Handbook of Physiology*, section 1, *The Nervous System*, vol. II, *Motor Control*, ed. BROOKS, V. B., pp. 509–595. American Physiological Society, Bethesda, MD, USA.

BECK, P. W., HANDWERKER, H.-O. & ZIMMERMANN, M. (1974). Nervous outflow from the cat's foot during noxious radiant heat stimulation. *Brain Research* **67**, 373–386.

BEHRENDS, T., SCHOMBURG, E. D. & STEFFENS, H. (1983). Facilitatory interaction between cutaneous afferents from low threshold mechanoreceptors and nociceptors in segmental reflex pathways to $\alpha$-motoneurones. *Brain Research* **260**, 131–134.

BESSON, J. M. & CHAOUCH, A. (1987). Peripheral and spinal mechanisms of nociception. *Physiological Reviews* **67**, 67–186.

BURKE, R. E., RUDOMIN, P., VYKLICKY, L. & ZAJAC III, F. E. (1971). Primary afferent depolarization and flexion reflexes produced by radiant heat stimulation of the skin. *Journal of Physiology* **213**, 185–214.

CREED, R. S., DENNY-BROWN, D., ECCLES, J. C., LIDDELL, E. G. T. & SHERRINGTON, C. S. (1932). *Reflex Activity of the Spinal Cord.* Oxford University Press, London.

ECCLES, J. C., ECCLES, R. M. & LUNDBERG, A. (1957). Synaptic actions on motoneurones caused by impulses in Golgi tendon organ afferents. *Journal of Physiology* **138**, 227–252.

ECCLES, J. C., MAGNI, F. & WILLIS, W. D. (1962). Depolarization of central terminals of group I afferent fibres from muscle. *Journal of Physiology* **160**, 62–93.

ECCLES, R. M. & LUNDBERG, A. (1959). Synaptic actions in motoneurones by afferents which may evoke the flexion reflex. *Archives Italiennes de Biologie* **97**, 199–221.

FEDINA, L. & HULTBORN, H. (1972). Facilitation from ipsilateral primary afferents of interneuronal transmission in the Ia inhibitory pathway to motoneurones. *Acta Physiologica Scandinavica* **86**, 59–81.

FITZGERALD, M. & LYNN, B. (1977). The sensitization of high threshold mechanoreceptors with myelinated axons by repeated heating. *Journal of Physiology* **265**, 549–563.

GRILLNER, S. & HONGO, T. (1972). Vestibulospinal effects on motoneurones and interneurones in the lumbosacral cord. *Progress in Brain Research* **37**, 243–262.

HARRISON, P. J. & JANKOWSKA, E. (1985). Sources of input to interneurones mediating group I non-reciprocal inhibition of motoneurones in the cat. *Journal of Physiology* **361**, 379–401.

HARRISON, P. J., JANKOWSKA, E. & ZYTNICKI, D. (1986). Lamina VIII interneurones interposed in crossed reflex pathways in the cat. *Journal of Physiology* **371**, 147–166.

HOLMQVIST, B. (1961). Crossed spinal reflex actions evoked by volleys in somatic afferents. *Acta Physiologica Scandinavica* **52**, suppl. 181, 1–67.

HOMQVIST, B. & LUNDBERG, A. (1961). Differential supraspinal control of synaptic actions evoked by volleys in the flexion reflex afferents in alpha motoneurones. *Acta Physiologica Scandinavica* **54**, suppl. 186, 1–51.

HULTBORN, H. (1972). Convergence on interneurones in the reciprocal Ia inhibitory pathway to motoneurones. *Acta Physiologica Scandinavica* **85**, suppl. 375, 1–42.

HULTBORN, H. (1976). Transmission in the pathway of reciprocal Ia inhibition to motoneurones and its control during the tonic stretch reflex. *Progress in Brain Research* **44**, 235–255.

HULTBORN, H., ILLERT, M. & SANTINI, M. (1976). Convergence on interneurones mediating the reciprocal Ia inhibition of motoneurones. II. Effects from segmental flexor reflex pathways. *Acta Physiologica Scandinavica* **96**, 193–201.

JÄNIG, W. & ZIMMERMANN, M. (1971). Presynaptic depolarization of myelinated afferent fibres evoked by stimulation of cutaneous C fibres. *Journal of Physiology* **214**, 29–50.

JANKOWSKA, E. (1992). Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology* **38**, 335–378.

JANKOWSKA, E. & LUNDBERG, A. (1981). Interneurones in the spinal cord. *Trends in Neurosciences* **4**, 230–233.

JANKOWSKA, E. & MCCREA, D. A. (1983). Shared reflex pathways from Ib tendon organ afferents and Ia muscle spindle afferents in the cat. *Journal of Physiology* **338**, 99–111.

KIRKWOOD, P. A., SCHOMBURG, E. D. & STEFFENS, H. (1987). Facilitatory interaction in spinal reflex pathways from nociceptive cutaneous afferents and identified secondary spindle afferents in the cat. *Experimental Brain Research* **68**, 657–660.

KNIFFKI, K.-D., SCHOMBURG, E. D. & STEFFENS, H. (1981). Effects from fine muscle and cutaneous afferents on spinal locomotion in cats. *Journal of Physiology* **319**, 543–554.

LUNDBERG, A. (1969). Convergence of excitatory and inhibitory action on interneurones in the spinal cord. In *The Interneurone*, UCLA Forum Medical Sciences No. 11, ed. BRAZIER, M. A. B., pp. 231–265. University of California Press, Los Angeles.

LUNDBERG, A. (1975). Control of spinal mechanisms from the brain. In *The Nervous System*, vol. 1, *The Basic Neurosciences*, ed. TOWER, D. B., pp. 253–265. Raven Press, New York.

LUNDBERG, A. (1979). Multisensory control of reflex pathways. *Progress in Brain Research* **50**, 11–28.

LUNDBERG, A. (1982). Inhibitory control from the brain stem of transmission from primary afferents to motoneurones, primary afferent terminals and ascending pathways. In *Brain Stem Control of Spinal Mechanisms*, ed. SJÖLUND, B. & BJÖRKLUND, A., pp. 179–224. Elsevier, Amsterdam.

LUNDBERG, A., MALMGREN, K. & SCHOMBURG, E. D. (1977). Cutaneous facilitation of transmission in reflex pathways from Ib afferents to motoneurones. *Journal of Physiology* **265**, 763–780.

LUNDBERG, A., MALMGREN, K. & SCHOMBURG, E. D. (1978). Role of joint afferents in motor control exemplified by effects on reflex pathways from Ib afferents. *Journal of Physiology* **284**, 327–343.

LUNDBERG, A., MALMGREN, K. & SCHOMBURG, E. D. (1987*a*). Reflex pathways from group II muscle afferents. 1. Distribution and linkage of reflex actions to α-motoneurones. *Experimental Brain Research* **65**, 271–281.

LUNDBERG, A., MALMGREN, K. & SCHOMBURG, E. D. (1987*b*). Reflex pathways from group II muscle afferents. 2. Functional characteristics of reflex pathways to α-motoneurones. *Experimental Brain Research* **65**, 282–293.

LUNDBERG, A., MALMGREN, K. & SCHOMBURG, E. D. (1987*c*). Reflex pathways from group II muscle afferents. 3. Secondary spindle afferents and the FRA: a new hypothesis. *Experimental Brain Research* **65**, 294–306.

SCHMIDT, P. F., SCHOMBURG, E. D., STEFFENS, H., STROHMEYER, A. & WADA, N. (1987). A nociceptive non-FRA pathway to plantaris motoneurones in the cat. *Journal of Physiology* **390**, 49*P*.

SCHOMBURG, E. D. (1988). Zur Funktion nozizeptiver Afferenzen in der spinalen Motorik. In *Schmerz und Sport*, ed. SPINTGE, R. & DROH, R., pp. 207–219. Springer, Berlin, Heidelberg.

SCHOMBURG, E. D. (1990). Spinal sensorimotor systems and their supraspinal control. *Neuroscience Research* **7**, 265–340.

SCHOMBURG, E. D. (1991). The role of nociceptive afferents and enkephalins in spinal motor control. In *Restorative Neurology*, vol. 5, ed. WERNIG, A., pp. 345–353. Elsevier, Amsterdam.

SCHOMBURG, E. D. & STEFFENS, H. (1986). Synaptic responses of lumbar $\alpha$-motoneurones to selective stimulation of cutaneous nociceptors and low threshold mechanoreceptors in spinal cat. *Experimental Brain Research* **62**, 335–342.

SCHOMBURG, E. D., STEFFENS, H. & WARNEKE, G. (1986). Functional organization of the spinal reflex pathways from forelimb afferents to hindlimb motoneurones in the cat. II. Conditions of the interneuronal connections. *Brain Research* **375**, 280–290.

SHERRINGTON, C. S. (1903). Qualitative difference of spinal reflex corresponding with qualitative difference of cutaneous stimulus. *Journal of Physiology* **30**, 39–46.

WHITEHORN, D. & BURGESS, P. R. (1973). Changes in polarization of central branches of myelinated mechanoreceptor and nociceptor fibers during noxious and innocuous stimulation of the skin. *Journal of Neurophysiology* **36**, 226–237.

WILLIS, W. D. (1985). *The Pain System. The Neural Basis of Nociceptive Transmission in the Mammalian Nervous System*. Karger, New York.