Brain Research, 201 (1980) 465–470

Human nociceptive reactions: effects of spatial summation of afferent input from relatively large diameter fibers

JEAN CLAUDE WILLER, FRANÇOIS BOUREAU and DENISE ALBE-FESSARD

Laboratoire de Physiologie, Faculté de Médecine Saint-Antoine, 27 rue Chaligny, 75571 Paris Cedex 12 and (D A-F.) Laboratoire de Physiologie des Centres Nerveux, Université Paris VI, 75005 Paris (France)

(Accepted July 17th, 1980)

Key words: spatial summation — large diameter afferents — pain — flexion reflex — man

In a previous report[13], we observed that repetitive stimulation of relatively large diameter (A$\alpha\beta$) fibers of cutaneous nerves in man, evoked both pain sensation and nociceptive type of flexor reflexes (RIII). These results pointed out the importance of temporal summation in the genesis of pain and of the associated nociceptive motor responses initiated by such input[10,13]. In contrast to the numerous reports on spatial summation of unmyelinated afferent input[3–5,7,8], the role of spatial summation for myelinated afferent excitation for human nociceptive responses has not been adequately described. For this reason, we undertook to analyze spatial interactions in myelinated afferent input of cutaneous origin for human flexor reflexes of the lower limb and subjective sensations.

Experiments were carried out on 15 healthy volunteers (9 men, 6 women, 22–36 years of age) who previously had participated in similar experiments and were familiar with the experimental procedures. The subjects were carefully briefed before the sessions so as to avoid any element of surprise or of anxiety[11]. During the sessions, they sat comfortably in an armchair, in a state of muscular relaxation. The details for stimulating cutaneous nerves, recording sensory action potentials (SAP), reflex activities from flexor muscles and for measuring subjective sensations are described in previous papers[6,12,13]. Briefly, sural and peroneal superficialis (PS) nerves were stimulated with surface electrodes, while SAPs were recorded using needle electrodes as shown in Fig. 1. Reflexly evoked activity was recorded from a knee-flexor muscle: the biceps femoris (Bi), using a pair of surface electrodes placed on scratched and degreased skin over the muscle.

Fig. 1 shows the experimental arrangement. The electrical stimulation, according to the need, consisted either of a single rectangular pulse (0.01 to 0.5 msec duration), a single burst of 8–10 pulses delivered over 30 msec at a frequency of 100 or 300 Hz, or a double stimulation (train–train) with a variable time delay from 10 to 900 msec. In all cases, the stimulation was carefully measured with a current probe connec-

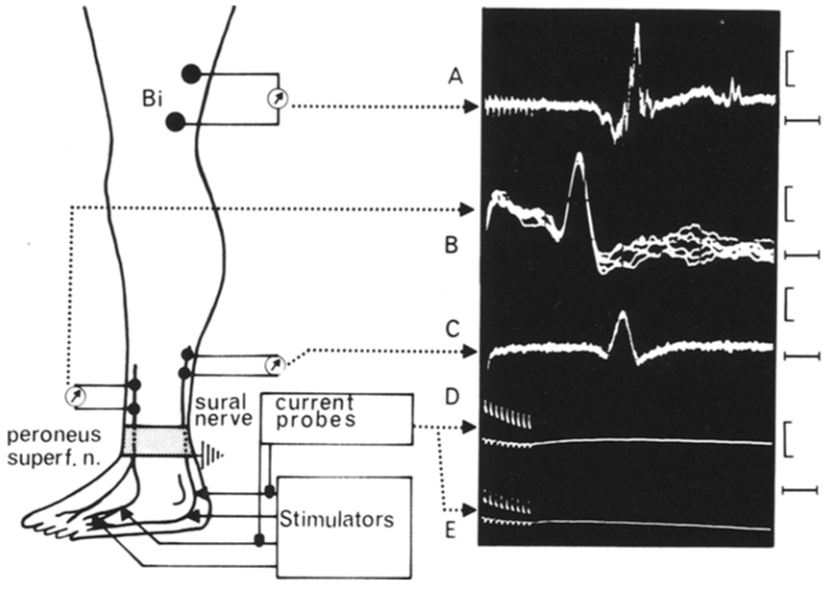

Fig. 1. Experimental arrangement for stimulating and recording the afferent volleys of the sural and peroneal superficialis nerves, the reflex activities from the biceps femoris muscle (Bi) and for measuring the intensities of stimulation (current probes). Examples of recordings are shown in the right part of the figure. Calibration: A, 20 msec, 200 μV; B and C, 2 msec, 10 μV; D and E, 20 msec, 10 mA.

ted to the stimulating circuits and displayed on a storage oscilloscope, along with electrophysiological signals from cutaneous nerves and from the flexor muscle. The signals were also stored on magnetic tape and fed into an integrator circuit; the latter's output was displayed continuously by a pen recorder, permitting quantification of each response. The temperature of the room (20 $\pm$ 1 °C) and of the skin (33 $\pm$ 1 °C) near the stimulating and recording electrodes remained stable. The sensations reported by the subjects were measured using a rating scale[12]: the quality (tactile and painful) and the intensity of the electrically induced sensations were marked by each subject along a 10 cm line (representing the sensation scale), along which each subject had to indicate the type and intensity of his sensation. The left part of the scale turned out to represent tactile sensations while the extreme right corresponded to intense and unbearable pain. The pain threshold marked by the subjects was located somewhere in an intermediate region between these two poles. However, some precautions detailed elsewhere[12] were necessary to make this method reliable. The pain threshold was then determined using the staircase limits method, by series of progressively increasing and progressively decreasing stimulation intensities; it was noted in arbitrary units (au) on the scale which extended from 0 to 10. The threshold of the flexion reflex was chosen as the stimulus intensity which elicited a reflex 80 to 90% of the time. The reflex activity and the corresponding pain sensation elicited at threshold or at suprathreshold (when necessary) by repetitive stimulation of the relatively large diameter fibers of the sural nerve were then studied under two conditions: (a) when conditioned by repetitive PS nerve stimulation exciting similar diameter fibers of this nerve, that by itself elicited a

sensation of pain and nociceptive Bi reflexes; and (b) when conditioned by repetitive PS nerve stimulation (trains varying in duration from 30 to 80 msec) that by itself elicited only tactile or tickling sensations in the receptive field of this nerve (dorsal aspect of the foot and base of the second, third and fourth toes). The conditioning trains were applied synchronously or up to 900 msec prior to the test sural stimulation. Each test of a conditioning effect lasted 2 min and was repeated randomly 4–5 times during a given session. A test was preceded by a control period of 2–3 min. Each subject was tested a minimum of 3 times at one week intervals.

Under our experimental conditions, spatial summation by itself (synchronous stimulation of the PS and sural nerves) neither produced a significant change in pain sensation nor in the reflex activity compared to that elicited by sural stimulation alone. The lack of effect from synchronous stimulation held for a given subject in repeated sessions or for the group taken as a whole. In contrast, spatial summation associated with a temporal factor, using a variable time delay between the conditioning and the test stimulations resulted in facilitatory or in suppressive effects on both pain sensation and flexor reflex. The opposing effects were found to be dependent both on the intensity of the shock representing the conditioning stimulus (therefore on the composition of the afferent volley) and also on the time delay between the two stimuli.

The facilitatory effects were obtained when the sural (test) followed the PS (conditioning) stimulations with the intensity of both set at threshold for a report of pain (3 $\pm$ 1 au) and a RIII flexor reflex (10 $\pm$ 1.2 mA). The subjects reported an increase in pain sensation which reached a maximum (8.5 $\pm$ 1.5 au) at delay between 70 and 170

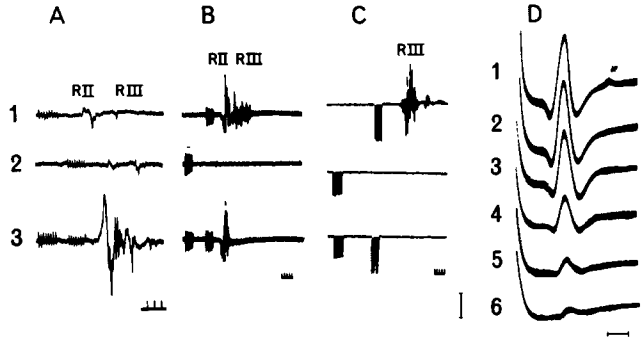

Fig. 2. Effects of a conditioning volley in A$\alpha\beta$ peroneal superficialis (PS) fibers on the RIII flexion reflex of the biceps femoris (Bi) evoked by the stimulation of the A$\alpha\beta$ fibers of sural nerve. In all cases, trains of electrical pulses were used. A: a facilitatory effect is obtained when both stimuli recruit 80 to 90% of the maximal amplitude of the A$\alpha\beta$ component of the neurogram (2 or 3 in D). B and C: suppressive effects are produced when prior to the sural nerve volley (90% of the A$\alpha\beta$ group), a PS volley of 40 to 50% of the maximal amplitude of the A$\alpha\beta$ wave is presented (4, 5, 6 in D). Note that in B, the RII reflex is present and absent in C. D: changes in the compound action potential recorded from the PS nerve as the intensity is progressively altered. Stimulus intensity varies from 50 mA in 1–4 mA in 6. Note in 1 the presence of the Aδ deflexion (arrow). This level was never used in these experiments. First deflexion corresponds to fibers with maximal conduction velocity of 55 m/sec and the beginning of the second deflexion (Aδ) to 22 m/sec. In B, C, and D, each trace is composed of the superimposition of 6 to 8 responses. Calibrations: horizontal: A, B and C, 10 msec; D, 2 msec. Vertical: A, B and C, 100 μV; D, 20 μV.

msec (Fig. 3A). Analysis of the subjective sensations showed that the increased pain elicited by such a double stimulation was reported particularly distally in the field of the sural nerve (base of the fifth toe) and distally in the field of PS nerve, where the innervations overlapped. The change in amplitude of the flexion reflex activity followed closely the change in reported pain sensation. As shown in Fig. 2A, at certain intervals, the two liminal (for pain and RIII reflex) stimulations combined to cause a substantial increase in the flexion reflex activity (RII and RIII) of the flexor muscle. This increase reached a maximum ($+70 \pm 20\%$; $t = 6.33$; df $= 58$; $P < 0.001$) between 60 and 160 msec, decreased progressively (as did the pain sensation) with a

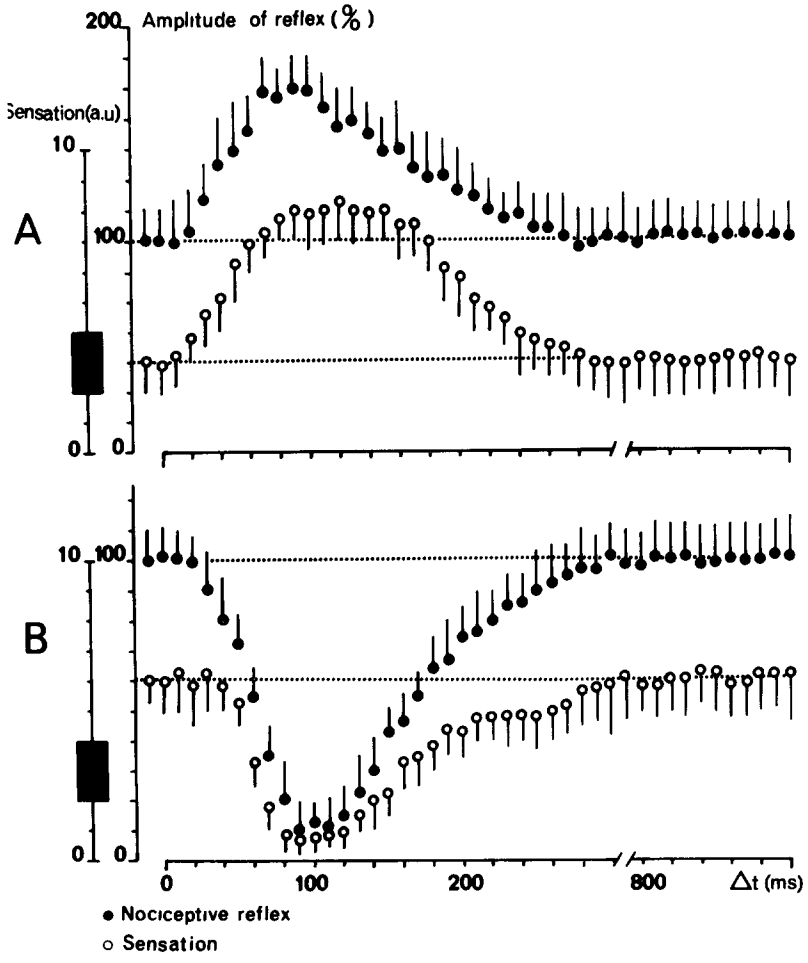

Fig. 3. Pooled results illustrating the time course of the facilitatory (A) and depressive (B) effects on reported pain (○) and on the RIII reflex (●) resulting from peroneal superficialis conditioning of the effects evoked by sural stimulation. Abscissa: time interval between the conditioning (PS) and the test (sural) stimulus. Ordinates: 1, amplitude of the integrated reflex responses expressed in % (100% corresponds to the mean of 100 control responses); 2, intensity of perceived sensation from 0 to 10 in arbitrary units (au) on the sensation scale (see text) The black area corresponds to the pain threshold (3 ± 1 au). Each point represents the mean and S.D. of 20 responses.

further increase in the delay, and returned to its control values at 230–300 msec (+10 ± 5%; $t = 0.25$; df = 58; ns) see Fig 3A. Recordings of the afferent volleys during these paired stimulations showed that to obtain the facilitatory effects, it was necessary to evoke at least 80% of the maximal amplitude of the first peak of the compoud action potential, i.e. 80% of the A$\alpha\beta$ component (Fig. 2D). Under the present condition, the Aδ component was never necessary, as was the case in a different experimental situation[13]. Moreover, the facilitatory effects just described cannot be attributed to peripheral modification of the afferent volleys since no change appeared either in the shape or in the amplitude of the sural compound action potential when the two stimuli were paired. It is of interest that reversing the test and the conditioning nerves gave similar results. When the reactions evoked by the PS nerve were employed as a test, using a stimulus intensity for liminal pain sensation and liminal flexion reflex in Bi, conditioning volleys of similar intensity from sural nerve enhanced pain and reflex activity at the same interstimulus intervals. Furthermore, the facilitated pain sensation was localized as before in the region of PS peripheral field and in the superposition of the receptive fields of these two nerves.

The depressive or inhibitory effects became evident when the conditioning PS nerve stimulus was chosen so as to evoke only a tactile sensation without eliciting any flexion reflex activity in Bi (Fig. 2B and C); this intensity corresponded to a partial recruitment of the largest fibers of PS nerve since the neurogram was found to consist of 50% of the maximal amplitude of the first component (Fig. 2D). The sural stimulation (test) was at an intensity (14 ± 1 mA) unequivocally suprathreshold for the nociceptive reflex as well as supraliminal for pain sensation (6 ± 0.7 au). At this stimulus intensity, the compound action potential had a maximum A$\alpha\beta$ wave without evident Aδ activity[13]. Under these conditions, in contrast to the facilitatory effects described above, the pain sensation and the nociceptive reflex decreased as a function of the time delay (Fig. 3B). The pain evoked by the test stimulation disappeared between 60 and 140 msec, giving place to a tactile sensation (1 ± 0.5 au), returning to its control values with stimulus intervals of 200–300 msec delay. The subjects compared this decrease in pain as a tactile curtain which was wrapped around the ankle of the foot and which masked the noxious stimulation. We found that increasing the duration of the tactile conditioning train (up to 80 msec), did not increase the suppressive effects. The variations in the reflex (RIII) parallelled those observed with sensations (Figs. 2B, C and 3B). For stimulus intervals varying between 70 and 170 msec, a powerful and very significant depression in the RIII reflex was observed (—90 ± 10%; $t = 8.29$; df = 68; $P < 0.001$). The time course of this depression was found to be similar to that of the decrease of pain sensation (Fig. 3B). It is probably pertinent that during the depression of the RIII reflex, the tactile one (RII) when observed, was often significantly increased (+13%; $t = 3.42$; df = 68; $P < 0.001$), see Fig. 2B. The RII reflex, described by Hugon[6] and by Willer[12] as a short latency (50–70 msec) and low threshold (5 ± 0.4 mA) exteroceptive reflex, was not seen in all subjects, presumably because it is strongly modulated by supraspinal influences[6,12]. One can rule out post-discharge hyperpolarization of the motoneurons involved in the RII responses as the cause of depression of the RIII reflex, by the presence of the effect when the RII response was

absent and no motoneuron discharge occurred (Fig. 2C). As was the case for the facilitatory effects, interchanging the test and conditioning nerves when using the weaker conditioning shocks gave the same inhibitory pattern.

In conclusion, it appears clear that spatial summation of input from relatively large diameter cutaneous afferents can produce facilitatory or suppressive effects on nociceptive messages at spinal level. However, this study suggests that these opposite actions depend on at least partially different components of the afferent nerves. The facilitatory effects apparently result from the slower A$\alpha\beta$ fibers that include some from nociceptors[1,9] while the inhibitory interactions originate in somewhat lower threshold, presumably more rapidly conducting fibers. The latter probably are afferent fibers from receptors excited by innocuous mechanical stimulation[2]. Such data may be important in pain therapy: it offers a possible explanation of some undesired hyperalgesias produced in patients with chronic pain when too intense stimuli are used for transcutaneous nerve stimulation.

We would like to thank Professor E. R. Perl for his kind and helpful contribution.

1 Burgess, P. R and Perl, E. R., Myelinated afferent fibres responding specifically to noxious stimulation of the skin, *J. Physiol (Lond.)*, 190 (1967) 541–562.
2 Burgess, P R. and Perl, E. R., Cutaneous mechanoreceptors and nociceptors. In A. Iggo (Ed), *Handbook of Sensory Physiology; Somatosensory System, Vol. 2*, Springer–Verlag, Berlin, 1973, pp. 29–78.
3 Chung, J. M. and Wurster, R. D., Neurophysiological evidence for spatial summation in the CNS from unmyelinated afferent fibers, *Brain Research*, 153 (1978) 596–601.
4 Greene, L. C. and Hardy, J. D , Spatial summation of pain, *J appl. Physiol.*, 13 (1958) 457–464.
5 Hardy, J. D. and Oppel, T. W , Studies in temperature sensation. III. The sensitivity of the body to heat and the spatial summation of the end organ responses, *J. clin. Invest.*, 16 (1937) 533–540.
6 Hugon, M., Exteroceptive reflexes to stimulation of the sural nerve in normal man. In J. E Desmedt (Ed), *New Developments in Electromyography and Clinical Neurophysiology, Vol. III*, Karger, Basel, 1973, pp. 713–729.
7 Marks, L E. and Stevens, J C., Spatial summation of warmth: influence of duration and configuration of the stimulus *Amer. J. Psychol.*, 86 (1973) 251–267
8 Marks, L. E. and Stevens, J. C., Interaction of spatial and temporal summation in the warmth sense, *Sens. Proc.*, 1 (1976) 87–98.
9 Perl, E. R., Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli, *J. Physiol. (Lond.)*, 197 (1968) 597–615.
10 Scherrer, J., Barbizet, J., Oudot, L. and Henaff, M., Contribution à l'étude de l'organisation temporo-spatiale de la sensibilité somesthésique normale *Ann psychol.*, 54 (1954) 53–81.
11 Willer, J. C., Influence de l'anticipation de la douleur sur les fréquences cardiaque et respiratoire et sur le réflexe nociceptif chez l'homme, *Physiol. Behav.*, 15 (1975) 411–415.
12 Willer, J C , Comparative study of perceived pain and nociceptive flexion reflex in man, *Pain*, 3 (1977) 69–80.
13 Willer, J. C., Boureau, F. and Albe-Fessard, D , Role of large diameter cutaneous afferents in transmission of nociceptive messages. electrophysiological study in man, *Brain Research* , 152 (1978) 358–364.