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EXCITATION AND SENSITIZATION OF FINE ARTICULAR AFFERENTS FROM CAT'S KNEE JOINT BY PROSTAGLANDIN E_2

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SUMMARY

1. In cats anaesthetized with α-chloralose extracellular recordings were made from fine afferent units belonging to the medial articular nerve of the knee joint. The excitatory and sensitizing effects on articular afferents of prostaglandin E_2 (PGE_2) applied intra-arterially close to the joint were examined.

2. Bolus injections of PGE_2 doses of 0·03–30 μg excited about 60% of both the group III (conduction velocity 2·5–20 m/s) and the group IV units (conduction velocity < 2·5 m/s). The duration and size of the responses were dose dependent consisting in most cases of low-frequency discharges which lasted up to several minutes. Excitation was found among afferents with low and high mechano-sensitivity.

3. Among the group III units PGE_2 sensitized 64% for their responses to movements and 50% for their responses to bradykinin (applied intra-arterially close to the joint). Sensitization did not depend on the mechanical threshold previous to chemical stimulation. Among the group IV units PGE_2 sensitized only 25% for their responses to movements but 75% for their reactions to bradykinin. In group IV fibres a low mechanical threshold predisposed for sensitization to movements and a higher threshold for sensitization to bradykinin.

4. Some units were sensitized and excited, others were either sensitized or excited and some units were not affected by PGE_2. We conclude that PGE_2 induces in a large proportion of fine articular afferents of normal joints discharges which are similar to those induced by an experimental inflammation. Thus PGE_2 may be an inflammatory mediator which has a major role in the generation of the afferent activity developing in the course of an arthritis.

INTRODUCTION

Inflamed tissue often contains high concentrations of different prostaglandins. Prostaglandin E_2 (PGE_2) in particular has been isolated from inflammatory exudates, e.g. of joints of patients suffering from rheumatoid arthritis (Thomas & West, 1973; Higgs, Vane, Hart & Wojtulewski, 1974; Trang, Granström & Lövgren, 1977; Brodie, Hensby, Parke & Gordon, 1980; Egg, Günther, Herold & Kerschbaumer, 1980; Bombardieri, Cattani, Crabattoni, DiMunno, Pasero, Patrono, Pinca & Pugliese, 1981; Higgs, Palmer, Eakins & Moncada, 1981; Salmon, Higgs, Vane,

Bitensky, Chayen, Henderson & Cashman, 1983). A high level of PGE_2 was also found in exudates of experimentally inflamed tissue including those of artificially inflamed joints (Willis, 1969; DiRosa, Giroud & Willoughby, 1971; Blackham, Farmer, Radziwonik & Westwick, 1974; Moncada, Ferreira & Vane, 1975; Higgs & Salmon, 1979; Holsapple, Schnur & Yim, 1980; Higgs & Moncada, 1983). It is assumed that prostaglandins play a significant role as mediators of inflammation, first, because they are produced locally in the early stage of an inflammatory lesion, second, because they dilate vessels and enhance the oedematous effect of other mediators, thus supporting the development of redness, warmth and oedema of the inflamed tissue (Juhlin & Michaelsson, 1969; Thomas & West, 1973; Lewis, Nelson & Sygrue, 1975; Dick, Grennan & Zeitlin, 1976; Johnston, Hay & Morat, 1976; Zeitlin & Grennan, 1976; Williams & Peck, 1977; Williams, 1979; Higgs *et al.* 1981; Higgs & Moncada, 1983).

Prostaglandins may also contribute to the fourth classical symptom of inflammation, the hyperalgesia or pain in the inflamed tissue. This effect was mainly attributed to their potency of enhancing the algesic action of other inflammatory mediators (Ferreira, 1972; Moncada *et al.* 1975; Ferreira, Nakamura & Castro, 1978; Ferreira & Nakamura, 1979; Tyers & Haywood, 1979; Higgs *et al.* 1981; Higgs & Moncada, 1983).

The aim of this investigation was to study the effect of prostaglandins on the discharge behaviour of single afferent fibres of cat's knee joint. It was carried out on the background of the experiments which were performed in this laboratory recently. These experiments yielded data on the changes in excitability which are induced in single afferents of articular nerves by an acute experimental arthritis. The major effects consisted of changes in responsiveness to mechanical stimuli and of changes in resting discharges. Low-threshold units with thin myelinated and unmyelinated axons displayed increased responses to movement stimuli. High-threshold afferents became sensitive to movements in the working range of the joint. In addition mechanosensitivity was induced in units without detectable sensitivity to mechanical stimuli in the normal tissue. Also resting activity was induced or increased as a consequence of arthritis. The relationship between these afferent discharges and the clinical symptoms of hyperalgesia and pain in an inflamed joint were discussed previously (Schaible & Schmidt, 1985, 1988; Grigg, Schaible & Schmidt, 1986).

In order to study the mechanisms underlying these phenomena we examined the effects of inflammatory mediators on single afferent units. Here we report the results obtained by application of prostaglandin E_2 (PGE_2) to the afferent endings in the joint. Some of the results have been published in preliminary communications (Heppelmann, Schaible & Schmidt, 1985; Schaible & Schmidt, 1987).

METHODS

General procedures. The experiments were performed on forty-seven cats of both sexes weighing 2·5–3·5 kg. Initially the animals were anaesthetized by an intramuscular injection of 15–20 mg/kg ketamine hydrochloride (Ketanest). After insertion of a catheter into the cephalic vein α-chloralose was given intravenously in a dose of 60–80 mg/kg. The trachea was cannulated to allow artificial respiration and another catheter was inserted into one carotid artery to measure blood pressure continuously. After this initial dissection the animal was ventilated artificially following

immobilization with pancuronium bromide (Pancuronium), 0·6 mg/h I.V. α-Chloralose was given in additional doses of 20 mg/kg to maintain a deep level of anaesthesia. Depth of narcosis was checked by observing the size of the pupils (they had to be closed) and by continuous control of blood pressure (if blood pressure was increased significantly during dissection, additional α-chloralose was administered before the operation was continued). Blood pressure, artificial respiration and body temperature were kept at physiological levels throughout the experiment.

Preparation. The dissection of the right leg, the setting up of the animal on the mounting table, the performance of stimulation and recording and the classification of the afferent units were described previously (Schaible & Schmidt, 1983*a*, *b*; Kanaka, Schaible & Schmidt, 1985). In short, the skin was incised on the medial aspect of the right thigh from the inguinal region to the knee joint. The sartorius muscle was removed to expose the medial articular nerve (MAN) and the adjoining vessels. A screw was fitted to the bone in the proximal third of the femur to fix the leg rigidly to the mounting table so that the lower leg could be flexed and extended in a horizontal plane. A small catheter was inserted retrogradely into the saphenous artery below the branching site of the saphenous and the medial genicular artery to inject substances intra-arterially close to the joint. The saphenous nerve was cut distally from this branching point and in the inguinal fossa. For electrical stimulation the branch(es) of MAN was (were) dissected free from the surrounding tissue for a length of several millimetres near the knee. For isolation a small piece of plastic was placed under the MAN and bipolar electrodes were inserted to stimulate the nerve. Recordings were performed from MAN units in small filaments of the saphenous nerve (MAN joints the saphenous nerve in the proximal third of the thigh). The stimulating electrodes were removed before movement stimulation of the knee was started. The skin flaps were sewn onto an oval metal ring to form a trough which was filled with warm paraffin oil. The leg rested on a support with the knee, hip and ankle joint in a semiflexed position.

Recording and data processing. Recordings of single units from the knee were performed extracellularly with a bipolar electrode. The MAN units in saphenous nerve (searched by electrical stimulation of MAN with a stimulus of 10 V amplitude and a duration of 0·5 ms) were classified according to conduction velocity into group II units (conducting faster than 21 m/s), group III units (conduction velocity between 2·5 and 20 m/s) and group IV units (conduction velocity less than 2·5 m/s). Amplified impulses were filtered and fed into a window discriminator, the output of which was processed by a computer (Olivetti M24) using a CED interface. We constructed peristimulus time histograms. In addition the impulses were monitored on magnetic tape for later off-line analysis and displayed on an oscilloscope screen to be photographed.

A potentiometer was fixed over the leg. A bar was connected to the lower limb to transduce the movements to an electronic device whose output displayed the performed movement. The analog signal was photographed from the oscilloscope screen together with the spike activity.

Stimulation of joint afferents. After electrical identification of a unit the joint tissue was probed with a glass rod to localize the receptive field. In some cases local thresholds were determined using von Frey hairs of different stiffness. Units without receptive fields (especially unmyelinated ones which could have been sympathetic efferents) were excluded from further analysis. Thereafter in most cases passive movements were performed in the knee to put the unit in one of the four sensitivity categories which were defined earlier (Schaible & Schmidt, 1983*b*). It was examined whether a unit was strongly (category 1) or weakly activated (category 2) by movements within the working range of the joint (extension and flexion starting from a semiflexed position, supination and pronation starting from various angles between extension and flexion) or whether it was only activated by noxious movements (category 3, supination and pronation against the resistance of the joint tissue) or even not activated by innocuous and noxious movements (category 4). If there was resting activity in the absence of intentional stimulation it was recorded to determine its baseline level.

Finally it was tested whether an intra-arterial bolus injection of twice isotonic KCl given into the catheter in the saphenous artery would excite the unit. As in the injections of the other substances a volume of 0·3 ml was filled into the catheter (it had a capacity of about 0·4 ml) and then the drug-containing fluid was pushed into the saphenous artery by injecting 1 ml Tyrode solution into the catheter. Thus the fluid was first injected retrogradely against the blood stream to the branching point of the saphenous and genicular arteries and then it was washed down into the joint by the blood flow. Units without a clear response to KCl (consisting normally of a short burst of impulses) were excluded from further testing.

The investigation of the effects of prostaglandin E_2 (PGE_2) was performed in three different ways. In one series we injected solely PGE_2 intra-arterially to test excitatory effects evoked by this substance. In most cases we started with a dose of 0·03 μg (0·3 ml of a solution containing $2{\cdot}8 \times 10^{-7}$ mol/l) and continued with doses of 0·3, 3 and 30 μg PGE_2 (solutions of $2{\cdot}8 \times 10^{-6}$, $2{\cdot}8 \times 10^{-5}$ and $2{\cdot}8 \times 10^{-4}$ mol/l). Activity was displayed in peristimulus time histograms. In another series we injected first bradykinin repeatedly and tested whether an intermittent injection of PGE_2 would enhance the effects of bradykinin. Often several combinations of doses of PGE_2 and

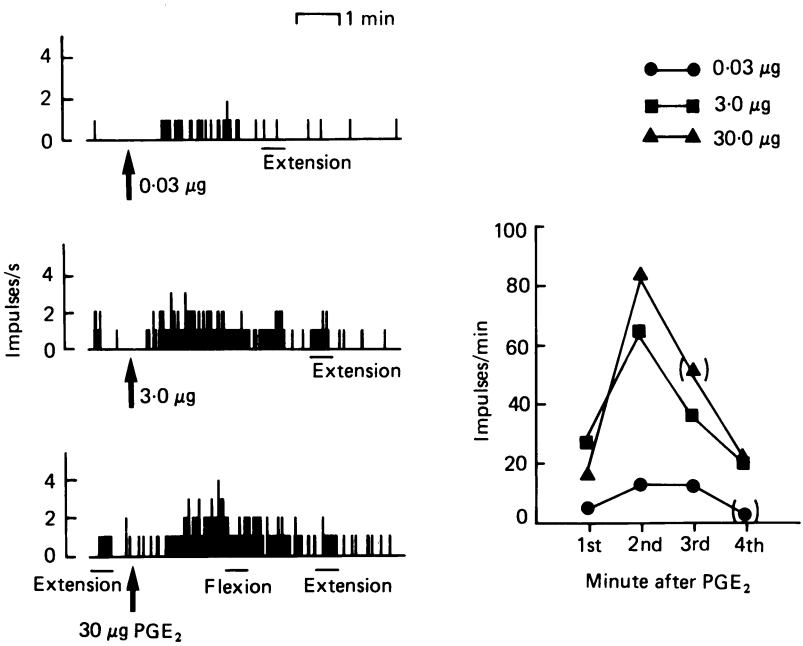

Fig. 1. Excitation of a low-threshold articular group III unit by PGE_2. On the left the responses to three different doses of PGE_2 are shown in peristimulus time histograms (address advance time 1 s). This unit was tested also for sensitization to movements. Some test movements (indicated by bars) are seen on the histograms. On the right these excitatory effects are quantified. The impulses in the first four minutes after the injections were counted. The symbols in parentheses show the number of impulses in minutes in which test movements were performed.

bradykinin were tried. In a third series we examined whether PGE_2 would change the mechanosensitivity of a unit. Here, several control movements in fixed intervals (2–5 min) were performed, then PGE_2 was injected intra-arterially and movements were performed as in the control period to register changes in the responses. In a few experiments the sensitization was tested, first, between PGE_2 and bradykinin, and second, between these drugs and movements.

RESULTS

Excitatory effects of prostaglandin E_2

In thirty-seven group III and twenty-eight group IV units we tested whether PGE_2 would lead to activity after the intra-arterial bolus injection. All of these units were sensitive to local mechanical stimulation of the joint. We found that more than half of the group III as well as of the group IV units responded to injections of prostaglandin. An excitation was found in twenty-two of thirty-seven group III (59·5%) and in seventeen of twenty-eight group IV units (60·7%) whereas fifteen

group III and eleven group IV units were not excited with doses of up to 30 μg (see Fig. 2*A* and *C*).

Responses to bolus injections of different amounts of PGE_2 are shown in Fig. 1. Typically, the responses started with a latency of about 10–30 s after beginning of the injection. The duration and the strength of the responses varied. Mostly a long-

TABLE 1. Threshold doses (T) of PGE_2 which were tested in twenty-two group III and eleven group IV units. Doses below 0·03 μg and higher than 30 μg were not tried

	Number of units	
	Group III	Group IV
Total	22	11
T = 0·03 μg	6	1
T = 0·3 μg	3	0
T = 3·0 μg	2	3
T = 30·0 μg	0	1
No excitation with 30·0 μg	11	6

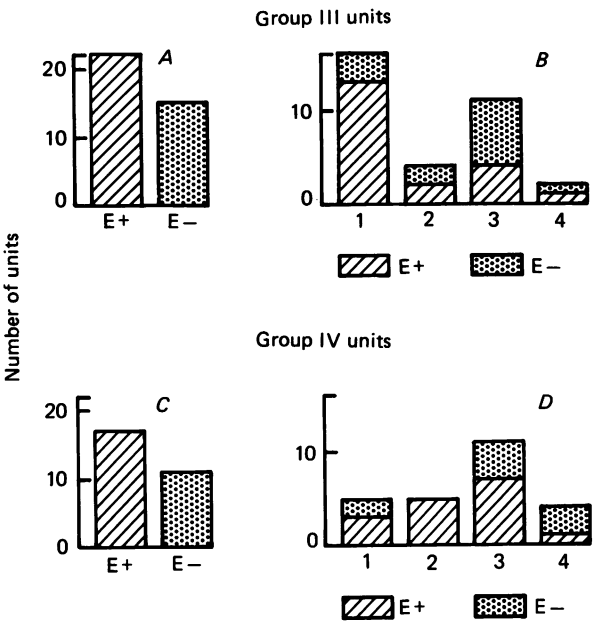

Fig. 2. Excitatory effect of 30 μg PGE_2 or less on group III and IV articular units. The number of units which were excited (E+) or not excited (E−) are shown in *A* and *C*. In *B* and *D* the excited (E+) and not excited (E−) units among afferents with different responsiveness to movements are illustrated. The numbers under the abscissa indicate the four categories of responsiveness. 1, strong excitation by innocuous movements, 2, weak excitation by innocuous movements, 3, excitation only by noxious movements, 4, no excitation by innocuous and noxious movements.

lasting reaction was evoked with a duration of at least 3 min provided the applied dose was high enough. In some units the activity did not return to the control level (which consisted of no spontaneous activity or low-frequency discharges) throughout the recording period. In others only few impulses were elicited even when 30 μg were applied (thus the response was of a short duration).

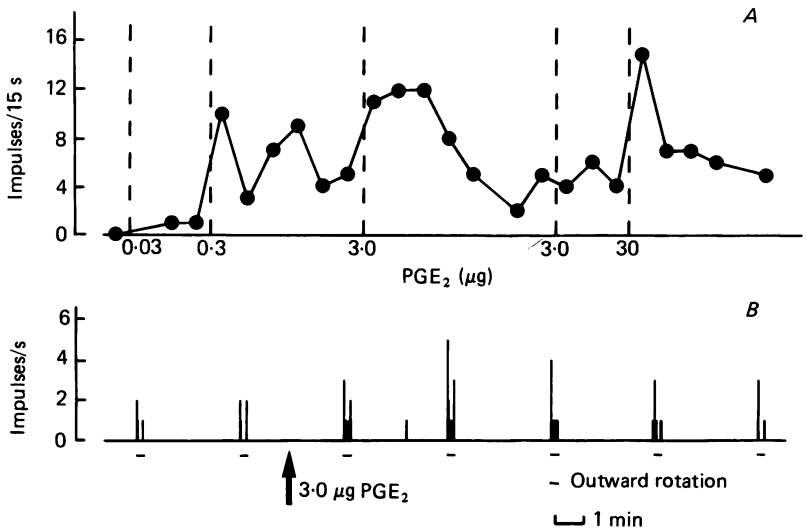

Fig. 3. Sensitization of a high-threshold group III unit for movements. *A*, responses to outward rotations prior to (no response) and after intra-arterial injections of different doses of PGE_2. The graph shows the whole recording time. Each outward rotation was kept for 15 s. With a few exceptions the movement was repeated every 4 min. *B*, peristimulus time histogram showing the effect of the first injection of 3 μg PGE_2. Prior to PGE_2 there was a small response; after PGE_2 the responses were enhanced for at least 14 min. PGE_2 did not excite this unit throughout the recording period.

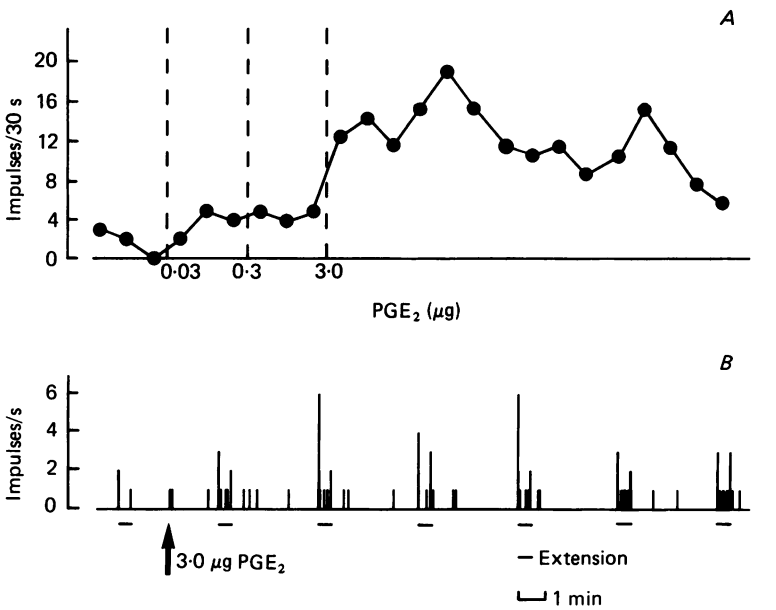

Fig. 4. Sensitization of a low-threshold group III unit for movements. Same type of illustration as in Fig. 3. The test movement was an extension, starting from the mid-position and kept constant for 30 s. The movements were repeated every 4 min. *A*, responses to the test movements prior to (small response) and after injections of PGE_2. *B*, the sensitizing effect of 3 μg PGE_2. After PGE_2 some discharges occurred in the intervals.

In twenty-two group III and eleven group IV units we tested the whole dose range from 0·03 to 30 μg. The threshold doses are displayed in Table 1. In the group III units the effective threshold seemed to be lower than in the group IV units. In the other units, which are also shown in Fig. 2*A* and *C*, we injected PGE_2 only in a dose of 3 and 30 μg and did not try the lower doses.

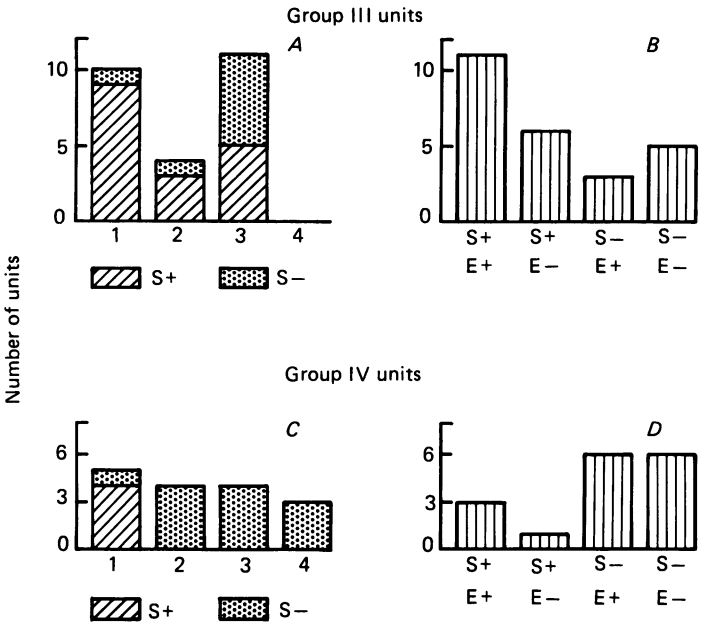

Fig. 5. Relationship between the mechanical threshold of group III (*A* and *B*) and group IV (*C* and *D*) units (categories 1–4) and the ability of PGE_2 to sensitize them for movements (*A* and *C*). In *B* and *D* is displayed that excitation (E+) and sensitization (S+) for movements could be combined or that only one effect or no effect was achieved.

In eleven units with threshold doses of less than 30 μg the relationship between dose and strength of response was studied. We found that in ten units the strength (and duration) of the responses were augmented when the applied dose was increased (see the recordings of the group III unit in Fig. 1). In one unit, however, such a relationship was not obvious. Repeated injections of the same dose led to tachyphylaxis in some of the afferents.

There was no relationship between the mechanical threshold for movements and the excitability to PGE_2 in this sample. Group III and IV units without responses to PGE_2 as well as units with responses to PGE_2 could belong to any of the four categories; they could be strongly or weakly excited by innocuous movements (categories 1 and 2), excited only by noxious movements (category 3) or even not excited by innocuous and noxious movements (category 4). This is illustrated in Fig. 2*B* and *D* for the units which could be classified according to their excitability by movements prior to the injection of PGE_2. Units without a response to PGE_2 could, however, be sensitized by PGE_2; others were not affected at all by PGE_2 (see below). Units which did not react to PGE_2 in doses of 0·03–30 μg possessed some chemosensitivity nevertheless. Six of seven units with a high threshold to movements

(four group III, two group IV units) and without response to PGE_2 were excited by bradykinin with threshold doses of 0·026 μg (two cases), 0·26 μg (three cases) and 2·6 μg (one case).

Sensitization by PGE_2 for mechanically evoked responses

A considerable number of the group III units could be sensitized by PGE_2 for their reaction to movements whereas among the group IV units such a sensitization was rare. Figure 3 shows the sensitization of a high-threshold group III unit by PGE_2. Initially this unit had a response to noxious movements but not to innocuous ones, i.e. it did not respond to the test movement, an innocuous outward rotation prior to PGE_2 (Fig. 3*A*). The injection of PGE_2 led to the appearance of reactions to this innocuous movement. Figure 3*A* shows the number of impulses which were elicited during outward rotation prior to and after the injections of PGE_2. In Fig. 3*B* the discharge pattern following sensitization by 3 μg is illustrated. From Fig. 3*A* it appears that the sensitization had a long duration (the interval between the movements was 4 min). In fact the unit showed increased sensitivity during the whole recording time. In this unit there was no direct excitation by PGE_2 (see Fig. 3*B*).

Figure 4 shows a group III unit with a low threshold to movements. Prior to PGE_2 it had a weak response to extension (Fig. 4*A*). The injection of PGE_2 led to an increase of the responses to extension. The effect of 3 μg PGE_2 is displayed in Fig. 4*B*. As in the unit shown in Fig. 3 this fibre was also sensitized for a long time by the bolus injection. As the other unit it showed a positive relationship between the applied dose and extent and duration of the sensitization. During the intervals between the movements few impulses were noted after PGE_2.

Figure 5*A* and *C* shows the sensitizing effects in the whole population of the group III and IV units. A sensitization was found for most of the low-threshold group III units and for about half of the high-threshold group III ones. As mentioned above there was almost no effect in the group IV units. Figure 5*B* and *D* illustrates that the sensitization for movements could be combined with a direct excitation of the unit or that it could occur alone. Other units were only excited but not sensitized for movements (especially among the group IV units). The dose which was necessary to sensitize a unit could be higher than that which was necessary for its excitation; e.g. three group III units which were excited with 0·03 μg PGE_2 required doses of 0·3 and 3 μg to become sensitized (see Fig. 1*A*).

Sensitization by PGE_2 for the responses to bradykinin

In eighteen group III and sixteen group IV units we tested whether PGE_2 would sensitize the articular afferents for their responses to chemical stimulation with bradykinin (the effects of bradykinin have been described in detail in Kanaka *et al.* 1985). Sixteen of the group III and all of the group IV units had a response to bradykinin prior to the injection of PGE_2. In nine of the eighteen group III and in twelve of the sixteen group IV units a sensitization for bradykinin was found (Fig. 8*A* and *C*).

In Fig. 6 two units are illustrated. The histogram in Fig. 6*C* shows the response of a group III unit to an injection of bradykinin prior to the application of PGE_2. In Fig. 6*D* the response to the first injection of bradykinin after PGE_2 is displayed. It

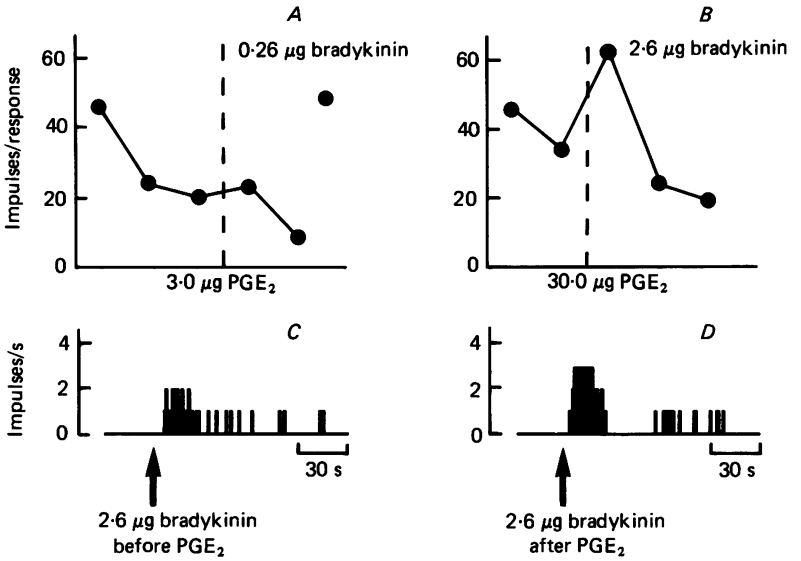

Fig. 6. Sensitization by PGE_2 of articular afferent units for bradykinin. The same group IV unit is shown in *A* and *B*, where different concentrations of bradykinin and PGE_2 were applied to study their interaction. The symbols show the number of impulses elicited by the bolus injections of bradykinin. The interval between the injections of bradykinin was 4 min. *C* and *D*, responses of a group III unit to bradykinin. The response prior to PGE_2 is shown in *C* and the response to the first injection of bradykinin 2 min after 30 μg PGE_2 in *D*.

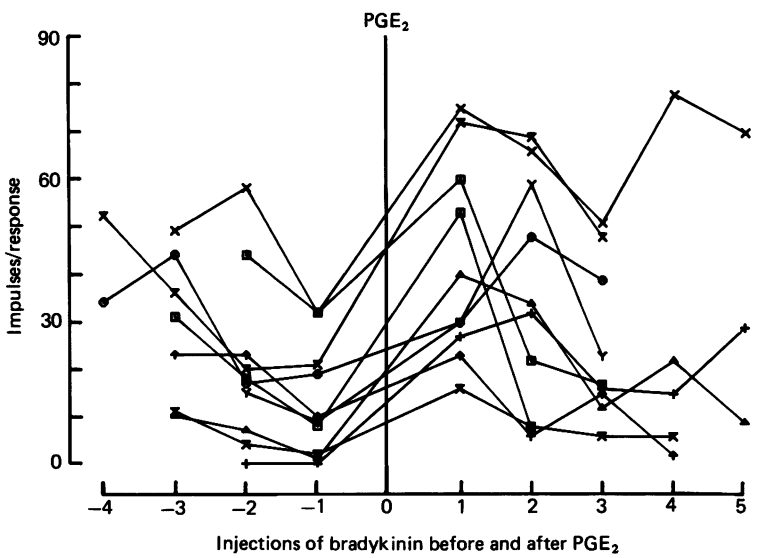

Fig. 7. Sensitization of group IV units to bradykinin by PGE_2. Each unit is characterized by a specific symbol. The numbers −5 to −1 indicate bradykinin injections prior to PGE_2, the numbers 1 to 5 those after PGE_2. The intervals between the injections of bradykinin were 3–5 min. The concentrations of bradykinin and PGE_2 were not identical for the whole sample of units. For each unit only the best sensitizing effect is displayed.

was clearly enhanced. In Fig. 6*A* and *B* is illustrated that such a sensitization was dependent on the doses of bradykinin and PGE_2. In Fig. 6*A* is shown a test series in a group IV unit with 0·26 μg bradykinin and 3·0 μg PGE_2. Typically the repeated injections of bradykinin during the control period yielded responses showing tachyphylaxis. The injection of PGE_2 did not lead to enhancement of the subsequent

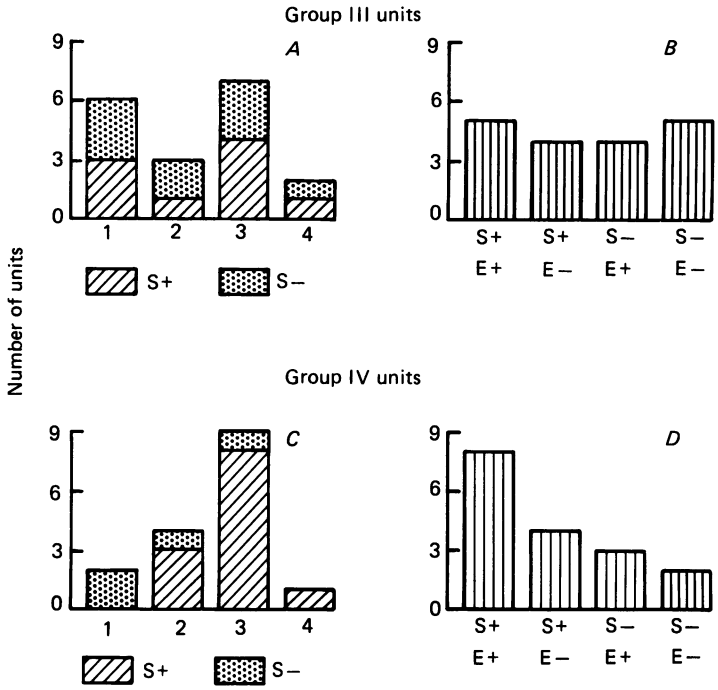

Fig. 8. Relationship between the mechanical threshold of group III and IV units (categories 1–4) and the ability of PGE_2 to sensitize them for responses to bradykinin (*A* and *C*). In *B* and *D* is illustrated that an excitatory (E+) and sensitizing effect (S+) could be combined or that only one effect or no effect could be observed.

reaction to bradykinin. When a combination of 2·6 μg bradykinin and 30·0 μg PGE_2 was used the same unit showed a clear enhancement of the response to bradykinin after PGE_2 (Fig. 6*B*). Similar results were obtained in most of the units which showed clear sensitization for bradykinin by PGE_2. In Fig. 7 the sensitization of ten group IV units is illustrated.

Figure 8*A* and *C* shows the relationship between the mechanical thresholds for movements of the units and the ability of PGE_2 to sensitize them for bradykinin. Among the group III units sensitization was found in units of all four categories. In the group IV population sensitization was observed for the units of categories 2, 3 and 4, but not for two units of category 1. From the comparison of Figs 8*C* and 5*C* it appears that PGE_2 is able to sensitize high-threshold group IV units for chemical stimulation but fails to sensitize them to respond to innocuous movements of the joint. Most of the group IV units of Fig. 7 were classified as belonging to category 3 thus being activated only by noxious movements.

In some afferents PGE_2 caused a sensitization for bradykinin and a direct

excitation. In other units PGE_2 had only a sensitizing effect for bradykinin but not an excitatory one and some afferents were only excited by PGE_2 but not sensitized for bradykinin. Few units were not affected at all by PGE_2. This is illustrated in Fig. 8*B* and *D*.

DISCUSSION

These results show that PGE_2 has several actions on fine afferents of the normal knee joint of the cat. In a large proportion of the units we observed direct excitation and/or sensitization for movements and/or sensitization for chemical stimulation with bradykinin. Other units were not affected at all by PGE_2. Excitatory and sensitizing effects could occur in combination or alone. The results will now be discussed on the background of our recent work on the effect of an acute inflammation on fine articular afferents.

The bolus injection of PGE_2 led to discharges in more than half of the group III and IV units of normal joints. In most cases this excitation lasted several minutes whereas that elicited by for example bradykinin had a short duration (most often less than 1 min) (Kanaka *et al.* 1985). The observation of long-lasting excitatory effects favours the idea that PGE_2 as an inflammatory mediator may contribute to the induction of ongoing discharges which are present in most group III and IV units from inflamed joints (Schaible & Schmidt, 1985; Grigg *et al.* 1986; Schaible & Schmidt, 1988).

An excitatory effect of PGE_2 was observed in units with different mechanosensitivity. Similarly, the experimental arthritis induced by kaolin and carrageenan induces ongoing discharges in group III and IV units of different mechanosensitivity (Schaible & Schmidt, 1988). Thus, from the long-lasting responses to PGE_2 and the non-selective excitatory potency we propose that part of the resting discharges in units from inflamed joints may be caused by PGE_2.

This assumption is supported by the observation that inhibitors of the prostaglandin synthesis reduced the discharges of units from inflamed joints and that a small amount of PGE_2 injected intra-arterially after such treatment may reverse this depressing effect (Heppelmann, Pfeffer, Schaible & Schmidt, 1986). In those experiments the bolus injections of 0·03 and 0·3 μg PGE_2 led to increases of resting discharges in groups III and IV units which lasted more than 15 min in most cases. In most units this excitatory action was combined with a sensitization for movements in the working range (Heppelmann *et al.* 1986). The very pronounced effects of PGE_2 in this situation may indicate that PGE_2 has also a dominant role in the maintenance of the resting discharges coming from the inflamed joint. Possibly, the level of PGE_2 may determine the discharge rate of units from inflamed joints.

On the other hand, some of the afferents of normal joints were not excited even with a high dose of PGE_2. The reason is not a general insensitivity for chemical stimulation because small doses of bradykinin also excite those units. Therefore, it may be assumed that single units possess different sensitivities for the excitatory effect of PGE_2, consisting of those with high sensitivity and others with no or low sensitivity. This hypothesis, however, can only be tested in a preparation where the concentration of PGE_2 at the receptive ending is known exactly. Unfortunately this is not possible in this type of experiment.

The second major effect of PGE_2 is the sensitization of fine articular afferents. In general this is well in agreement with numerous pharmacological and some physiological studies which revealed the sensitizing property of prostaglandins e.g. for the excitatory effects on afferents which are exerted by algesic substances like bradykinin and histamine (Ferreira, 1972; Moncada *et al.* 1975; Handwerker, 1976*a*; Chahl & Iggo, 1977; Tyers & Haywood, 1979; Higgs *et al.* 1981; Mense, 1981; Kumazawa & Mizumura, 1984). A sensitizing effect was also described for the responses to heat in polymodal nociceptors of skin (Handwerker, 1976*a*, *b*) and for responses to local mechanical stimulation in cutaneous Aδ nociceptors (Pateromichelakis & Rood, 1982). In most of these studies it was stated that PGE_2 may sensitize without having an excitatory effect. Our results show that the effect of PGE_2 on afferent units cannot be described in such general manner. First, units may be excited but lack any sign of sensitization; second, the sensitizing effect may be different for mechanical and chemical stimuli. To our surprise sensitization for movements was very obvious in group III units but almost absent in group IV ones. On the other hand, sensitization for bradykinin was very pronounced in group IV units, especially in those which could not be sensitized for movements (the high-threshold ones). Thus the failure of PGE_2 to sensitize these group IV units for movements is probably not the result of inadequate testing.

The arthritis evoked by kaolin and carrageenan leads to sensitization of groups III and IV units for movements: low-threshold units become more sensitive to movements in the working range of the joint, and units with a high threshold and those unresponsive to mechanical stimuli in the normal joint achieve during inflammation such a sensitivity that they also respond to movements in the working range (Schaible & Schmidt, 1985; Grigg *et al.* 1986; Schaible & Schmidt, 1988). As such an experimental inflammation is promoted by endogenous inflammatory mediators including PGE_2 (Willis, 1969; DiRosa *et al.* 1971; Blackham *et al.* 1974; Moncada *et al.* 1975; Higgs & Salmon, 1979; Holsapple *et al.* 1980; Higgs & Moncada, 1983) it may be assumed that these mediators also contribute to the sensitization of group III and IV units from inflamed joints. The present data show that PGE_2 is able to induce a long-lasting increase of sensitivity to movements in group III units including some of those having a high threshold to movements in the control period. Thus, in these units PGE_2 may play a major role in the sensitizing process. On the other hand, a considerable number of the group III units and almost all group IV units were not sensitized by PGE_2 in such a manner as observed during inflammation. There is the possibility that a bolus injection may not be sufficient to evoke this sensitization. But such an injection is able to sensitize units for bradykinin. Therefore, two other reasons for the lack of sensitization for movement stimuli are more likely. First, as for the excitatory effect, units may be differently predisposed for the sensitizing action of PGE_2; second, sensitization for mechanical stimuli may depend on the combined action of several mediators which are released during an inflammation.

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