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Review Article

Afferent and spinal mechanisms of joint pain

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I. Introduction

Joints are frequently affected by inflammatory and degenerative disorders and by injury. The major consequences of articular disorders are functional impairment of the joint, hyperalgesia and/or pain in the joint region. Joint pain may subside with restoration of the joint or with drug treatment and physical therapy. In many cases, however, joints remain a major source of chronic pain since the currently available therapies are not always satisfactory. Although detailed (clinical) observations of pain sensations in joints were made several decades ago, basic research investigating the neuronal mechanisms of nociception in the joint has only taken place in the last 10 years. Interest has recently been intensified and a number of laboratories have addressed different neurobiological aspects of articular disorders. Whereas signalling of nociceptive information (and pain) is an obvious function of the innervation of joints, a number of studies have provided evidence that the nervous system may also play a role in the pathogenesis of joint disorders through efferent neuronal mechanisms. Inflammation in joints, therefore, is a situation in which the complex functions of the nervous system can be studied in a clinically relevant painful pathological condition.

This article tries to summarize data on afferent and spinal mechanisms of nociception in the joint and on the efferent effects exerted by articular nerves on the joint. Since hyperalgesia and pain in joints are mainly associated with arthritis, emphasis will be put on neuronal changes that occur when joints are inflamed, and efferent effects of different neuronal systems will be described that may influence the inflammatory process. Fig. 1 gives an overview on the complex neurobiological events associated with inflammation and these will be addressed in some detail in the following sections. In the first part of this review, the basic anatomy and physiology of the neural components associated with joints are described along with changes which are known to occur during the development of joint inflammation. Fig. 1 shows the spinal cord as a centre for the integration of afferent information which can generate sensory, motor and sympathetic outputs. There is considerable functional plasticity in the spinal cord in arthritic conditions, suggesting a major contribution of

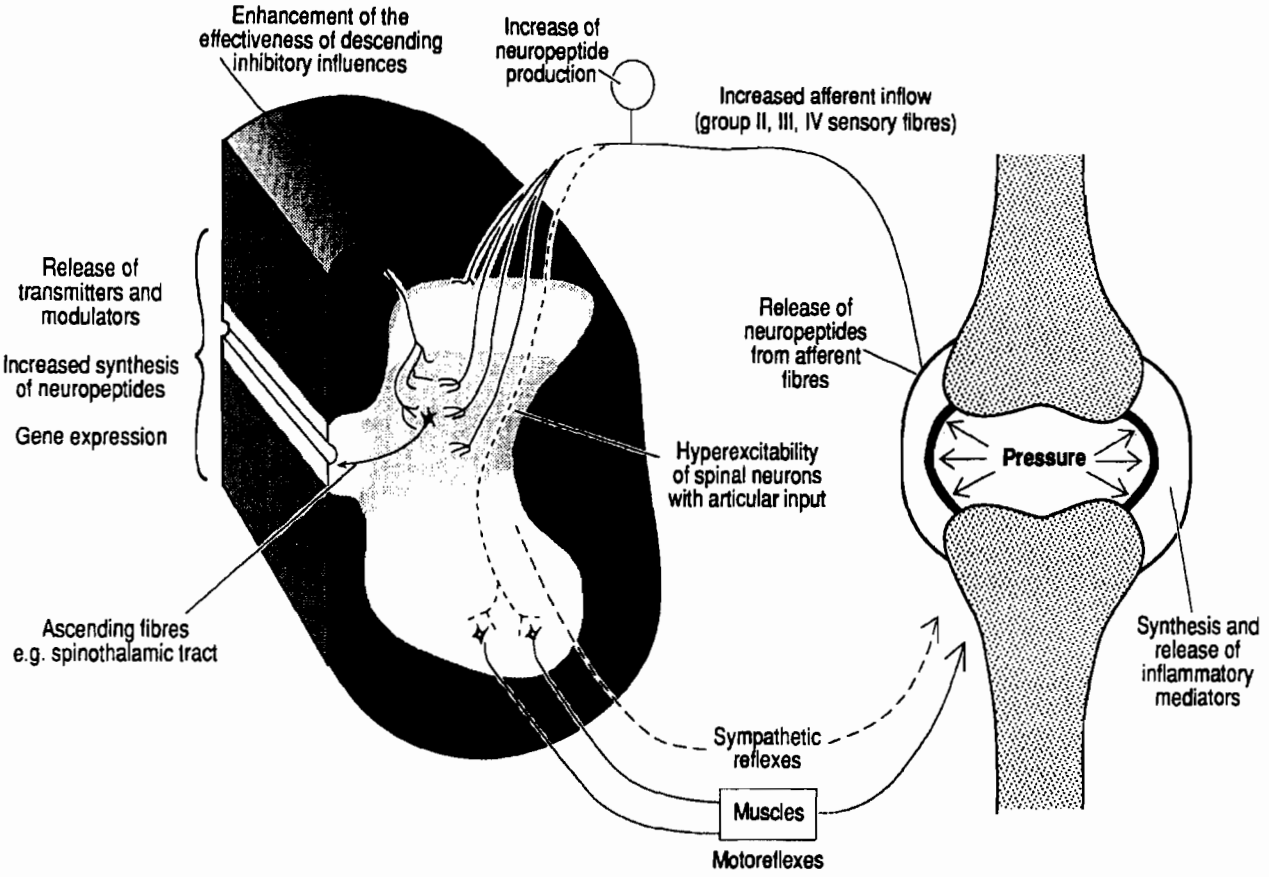

Fig. 1. Overview on neuronal events in the course of an inflammation in the joint.

the spinal cord to the expression of neuronal events following inflammation. Another major section will address, therefore, the neuronal and cellular events in the spinal cord associated with nociception in the normal and inflamed joint. Finally two sections will summarize data on motor reflexes involved in the nociception in joints and on sympathetic reflexes and their potential role in the expression of arthritic lesions.

I.A. Sensations in the joint

The major sensation that is ascribed to the joint is pain. It is questionable whether in daily life any other sensation is attributed to the joint itself. There is some evidence, however, that the afferent inflow from the joint is also involved in the sense of movement and position although muscular afferents seem to be more important. This matter will not be further discussed and the reader is referred to relevant review articles (Skoglund 1973; McCloskey 1978; Burgess et al. 1982; Darian-Smith 1984; Proske et al. 1988).

Some studies have been performed in humans to investigate the sensations which are elicited by stimulation of defined joint structures. Sensations of pain have been evoked when noxious mechanical, thermal and chemical stimuli such as acids and hypertonic salt solutions were applied to the fibrous structures of the joint, the ligaments and the fibrous capsule. By contrast the application of mechanical and thermal stimuli to the cartilage did not evoke sensations (see Lewis 1942; McEwen 1943; Kellgren and Samuel 1950). This is an interesting aspect since destructive processes in the cartilage often seem to be associated with pain, suggesting at first sight that cartilage is innervated. Although pain may be the most common sensation attributed to the joint, other sensations could be evoked in experimental situations. Punctate mechanical stimuli applied using a needle to capsule and ligaments were shown to evoke either the sensation of pain or pressure dependent on the site of the stimulation (Kellgren and Samuel 1950). These sensations were attributed to the innervation of the deep structures in the joints since the skin was anaesthetized. Interestingly not much evidence was provided about sensations evoked by stimulation of the synovial layer. In patients as well as in a trained volunteer the application of different mechanical stimuli to the synovial layer rarely evoked pain and other sensations (Kellgren and Samuel 1950). This

is another surprise since the synovial layer may be a major focus of painful inflammatory joint diseases.

Hyperalgesia and persistent pain in the joint are typical symptoms of inflammatory articular diseases. The nature of these pain sensations was described in a series of papers some 50 years ago. In most cases the pain is dull and badly localized (Lewis 1938, 1942; Kellgren 1939; McEwen 1943; Obletz et al. 1949; Kellgren and Samuel 1950). Lewis (1938) pointed out the similarity between pain in joints and muscles and the different character of these pain sensations compared to cutaneous pain. As a consequence he postulated separate pathways for nociceptive processes in cutaneous and deep somatic structures. Disease-associated pain in the joint may occur whilst the joint is kept immobile or 'unloaded' but characteristically the pain is induced or aggravated during movements and local mechanical stimulation of the affected joint, i.e., when the joint is loaded (weight-bearing) (Kellgren 1939; McEwen 1943).

I.B. Models of experimental inflammation in the joint

In order to study the neurobiological basis of arthritic pain and the involvement of neurogenic mechanisms in the pathogenesis of inflammatory lesions, models of experimental inflammation are necessary at some stage. In dogs, cats, rabbits, rats and pigeons acute forms of aseptic inflammation in the joint with swelling and cellular infiltration can be induced by the injection of crystals such as urate or kaolin and/or by injection of carrageenan into the cavity of a joint (Faires and McCarty 1962; Rosenthale et al. 1966; Brune et al. 1974; Schumacher et al. 1974; Santer et al. 1983; Okuda et al. 1984; Schaible and Schmidt, 1985, 1988a; Schaible et al. 1987b; Coderre and Wall 1987). These injections lead to the synthesis and release of inflammatory mediators which produce an oedema (see Moncada et al. 1979; Sedgwick and Willoughby 1985, and Section II.D.) and a rapid infiltration of polymorphnuclear granulocytes within the first hours (Santer et al. 1983). Within 1–3 h behavioural signs of hyperalgesia appear such as inactivation of the leg during walking and quick removal of the leg when the inflamed joint is pressed, suggesting a state of mechanical hyperalgesia. With time the acute inflammatory process may change its histopathological features and become more chronic (Santer et al. 1983).

Rat models based on the use of Freund's complete adjuvant (FCA), a suspension of heat-killed bacteria (e.g., *Mycobacterium tuberculosum* or *M. butyricum*) in mineral oil are commonly used to study the effect of chronic inflammation in joints. This type of arthritis has an immunological origin whereby an epitope contained on a mycobacterial heat shock protein (65 kDa) (Van Eden et al. 1989) is cross-reactive with a self-antigen in joint cartilage (Van Eden et al. 1985). This epitope is recognized by a rat T-cell clone which leads to a hypersensitivity reaction to the bacterial antigen and also to the cartilage proteoglycans (Van Eden et al. 1985). Since bacterial heat-shock proteins and the proteins in human cartilage show a degree of homology, it is thought that the type of antigen cross-reactivity seen in animal models might provide a basis for the initiation of autoimmune arthritis in humans (Van Eden et al. 1989).

Colpaert (1987) summarized expertimental data from behavioural studies indicating that adjuvant arthritis is associated with chronic pain. In its most severe form, FCA-induced polyarthritis, an injection of FCA into the foot pad, tail base or lymph nodes produces a 2-stage inflammatory reaction. In the first stage an acute local inflammatory reaction develops within the first few hours after inoculation but subsides after 3–5 days. During the second week a diffuse inflammatory reaction develops in the distal joints of the limbs. Lesions may also develop at other sites in the body, e.g., eyes, ears, tail, genitalia (see Pearson 1963; Billingham and Davies 1979). The inflammatory lesions usually subside after 4 weeks but may recur spontaneously at later times. The incidence and severity of FCA-induced polyarthritis is affected by several factors including the strain of animal used, the site of injection of FCA (e.g., foot pad, tail base, lymph nodes) and the composition of the adjuvant itself; several compounds have been added to the adjuvant to improve the incidence of the disease (Whitehouse et al. 1974) and these have been reviewed extensively elsewhere (Billingham and Davies 1979).

A less severe model of chronic joint inflammation is the FCA-induced monoarthritis (or unilateral adjuvant-induced inflammation). In this case only small amounts (100–150 μg *M. tuberculosum* or *M. butyricum*) of FCA are injected into the foot pad or into the skin overlying the ankle joint. This produces the local acute reaction but limits (Grubb et al. 1991; Butler et al. 1992) or abolishes (Iadarola et al. 1988a,b,c) the development of the secondary phase such that secondary lesions do not occur. The duration of the inflammatory lesion is restricted to between 2 and 4 weeks and there is no apparent gross physical impairment to the animal except at the inflamed site.

Due to their different pathology and time courses, both the acute and chronic models of joint inflammation have advantages and disadvantages. The chronic inflammation may produce all of the consequences of a chronic inflammatory pain state including neuronal, biochemical and immunhistochemical changes (see below) but the inflammation is not restricted to the joint. It may be difficult, therefore, to relate neuronal changes to the pathology of the joint itself. This is better controlled in models of acute inflammation which are

restricted to the afflicted joint. The acute form, however, will not exhibit those features which need days to develop.

II. Peripheral mechanisms

II.A. Anatomy and histology of the innervation of joints

II.A.1. Articular nerves

Joints are supplied by articular branches descending from main nerve trunks or their muscular, cutaneous and periosteal branches (see Polacek 1966). The articular nerves contain myelinated and unmyelinated sensory afferent fibres and unmyelinated efferent sympathetic postganglionic fibres (Gardner 1944; Skoglund 1956, 1973; Polacek 1966; Freeman and Wyke 1967a; Boyd and Davey 1968; Langford and Schmidt 1983). The total number of fibres and the proportions of afferent and efferent units in articular nerves has been determined by electron microscopy. For example, the medial and posterior articular nerves (MAN and PAN) supplying cat knee joint contain about 1200 fibres each (Langford and Schmidt 1983) whilst the PAN of rat knee contains about 400 axons (Hildebrand et al. 1991). Only 20% of the fibres in these nerves (and also in those of dog and monkey) are myelinated whereas about 80% are unmyelinated (Gardner and Lenn 1977; O'Connor and McConnanghey 1982; Langford and Schmidt 1983; Hildebrand al. 1991). Most myelinated units are small-diameter group III or Aδ fibres (conduction velocities between 2.5 and 20 m/sec) whereas relatively few are thick-diameter group II or Aβ units (with conduction velocities $>$ 20 m/sec) (Heppelmann et al. 1988; Hildebrand et al. 1991). About one-half of the unmyelinated fibres are sympathetic efferents since they were shown to disappear after surgical sympathectomy (Langford and Schmidt 1983; Hildebrand et al. 1991). A proportion of the afferent and efferent fibres in the joint nerves contain neuropeptides and this will be discussed below (see Section II.E.).

II.A.2. Types and location of receptive endings of articular afferents

Group II afferents are equipped with corpuscular endings of the Ruffini-, Golgi- and Pacini-type (Boyd and Davey 1968) and these are located in the fibrous capsule, articular ligaments, menisci and adjacent periosteum but not in the synovial tissue and the cartilage (see Johansson et al. 1991). By contrast group III and IV fibres terminate as non-corpuscular or 'free nerve endings' in the joint tissue. Non-corpuscular endings have been located in the fibrous capsule, adipose tissue, ligaments, menisci and periosteum using both light (Samuel 1952; Sklenska 1965; Frommer and Monroe 1966; Polacek 1966; Freeman and Wyke 1967a; Klineberg 1971) and electron microscopical methods (Halata et al. 1984; Heppelmann et al. 1990). The presence of non-corpuscular sensory nerve endings in the synovial layer (a major site of inflammatory foci in arthritic diseases) is, however, disputed. Although earlier reports described free nerve endings at this site (see summary in Polacek 1966) they have not subsequently been found using either the light (Gardner 1944; Samuel 1952; Freeman and Wyke 1967a; Halata and Groth 1976) or electron microscope (Halata and Groth 1976; Halata et al. 1984). Unmyelinated fibres have, however, been seen in close approximation to blood vessels in the synovial layer and this was related to sympathetic innervation (Gardner 1944; Samuel 1952; Freeman and Wyke 1967a). Recently the presence of sensory fibres in the synovial layer was again postulated since peptidergic structures have been identified in this region and the authors considered them to be afferent fibres (see Section II.E.).

II.A.3. Ultrastructure of non-corpuscular, free nerve endings

In a recent electron microscopic study the free nerve endings were visualized in some detail in the knee joint capsule of sympathectomized cats (Heppelmann et al. 1990). Group III and IV fibres formed terminal trees which consisted of a series of spindle-shaped thick segments connected by waist-like thin segments ('string-of-beads appearance'). These beads and the end bulb contained mitochondria, glycogen particles, vesicles and 'bare' areas of axolemma which were not covered by Schwann cell processes. The beads were assumed to represent multiple receptive sites. The relationship between the morphology of non-corpuscular endings and their functional receptive properties has not been shown.

II.B. Mechanoreceptive functions of articular afferents in the normal joint

Electrophysiological recordings have been mainly performed in the cat, rat and monkey. Initially the response properties of thick myelinated fast-conducting afferents of several joint nerves were investigated in order to define their functional role in the sensing of movements and position (Andrew and Dodt 1953; Boyd and Roberts 1953; Andrew 1954; Burgess and Clark, 1969; Klineberg 1971; Millar 1973, 1975; McCall et al. 1974; Clark 1975; Clark and Burgess 1975; Grigg 1975, 1976; Grigg and Greenspan, 1977; Carli et al. 1979; Tracey 1979; Ferrell 1980, 1985; Rossi and Grigg 1982; Shimamura et al. 1984; Nade et al. 1987; Dorn et al. 1991). More recently studies have been made using thin myelinated and unmyelinated afferent units in order to identify the afferent basis of nociception in the joint (Coggeshall et al. 1983; Schaible and Schmidt

1983a,b, 1988a,b; Guilbaud and Iggo 1985; Guilbaud et al. 1985; Kanaka et al. 1985; Grigg et al. 1986; Heppelmann et al. 1986; Russell et al. 1987; Neugebauer et al. 1989; He et al. 1990; Grubb et al. 1991; Schepelmann et al. 1992).

II.B.1. Classes of afferent fibres in regard to mechanical threshold

Afferent nerve fibres in the MAN and PAN of cat knee joint can be divided into several categories according to their activation threshold by mechanical stimuli. Fig. 2 shows the classification of mechanosensitive units by their responses to passive movements. Initially 4 categories were defined (Schaible and Schmidt 1983b). (1) Low-threshold units that were clearly activated by innocuous movements in the normal working range of the joint such as extension (ext.), flexion, inward rotation (IR) and outward rotation (OR) (Fig. 2A). Typically these units had stronger responses when noxious movements were applied, i.e., movements that were performed with appreciable torque against the resistance of the joint structures such as noxious outward rotation and noxious inward rotation (n.IR). These low-threshold units also responded to gentle pressure applied to the capsule and/or ligaments. (2) Units that were only weakly activated by innocuous movements (e.g., outward rotation, OR) but showed strong responses to noxious movements such as noxious outward rotation (n.OR) (Fig. 2B). (3) High-threshold units that were only activated by noxious movements but did not show any response to innocuous movements (Fig. 2C). When local mechanical stimuli were applied strong pressure was required to activate these units. (4) Afferents that were only activated by noxious pressure but did not respond to innocuous and noxious movements (Fig. 2D). Subsequent work revealed that another group of afferents had to be added, namely the group of 'mechano-insensitive afferents'. The latter group of afferents is activated by electrical stimulation of the axons and the intra-arterial injection of potassium chloride but they are neither activated by strong pressure nor by innocuous and noxious movements applied to the normal joint (Grigg et al. 1986; Schaible and Schmidt 1988a). Fibres which were unresponsive to mechanical stimulation of noxious intensities were also identified in cutaneous nerves (Bessou and Perl 1969; Lynn and Carpenter 1982; Handwerker et al. 1991; Meyer et al. 1991; Kress et al. 1992) and in visceral nerves (Häbler et al. 1988). 'Mechano-insensitive' articular afferents do not seem to be relevant for the encoding of mechanical stimuli in the normal joint but they may be important for mechanoreception during inflammatory lesions ('silent nociceptors'). They will be addressed in more detail in Section II.C.

Fig. 3 shows the proportions of group II, III and IV fibres in the different sensitivity classes in the MAN of cat knee joint (modified from Schaible and Schmidt

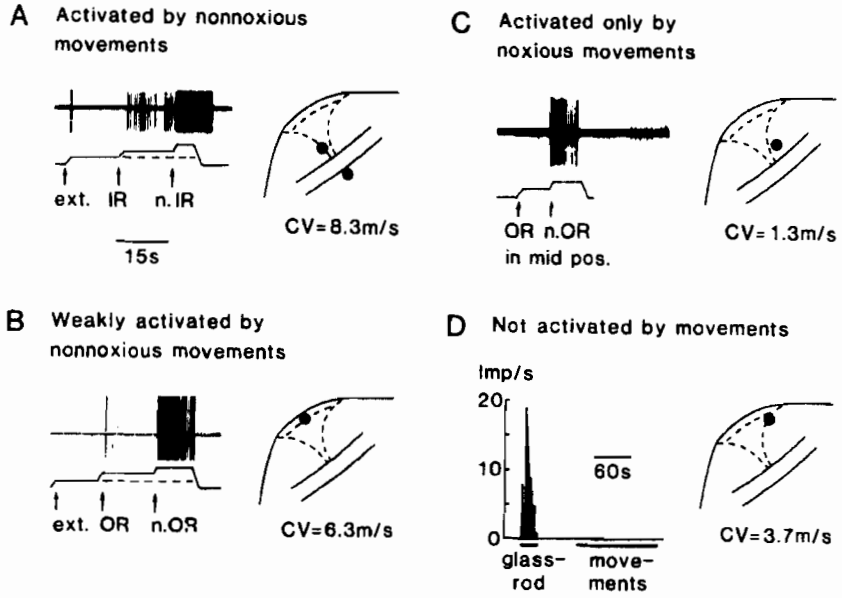

Fig. 2. Classes of articular afferents judged from the responses of these units to passive movements of the knee joint. A–D: insets on the right show the medial aspect of the knee joint and dots show the receptive fields of the units whose activity (action potentials) is displayed in the records. The traces below the specimen in A–C show the movements and altered positions. The units are also characterized by their conduction velocities (CV). The time scale in A applies also to B and C. Ext., extension; IR, innocuous inward rotation (pronation); OR, innocuous outward rotation (supination); n.IR and n.OR., noxious inward and outward rotation; mid pos., mid position, i.e., resting position between flexion and extension. In A and B the joint was first extended and then pronated (in A) or supinated (in B). D: the activity is shown in a peristimulus time histogram.

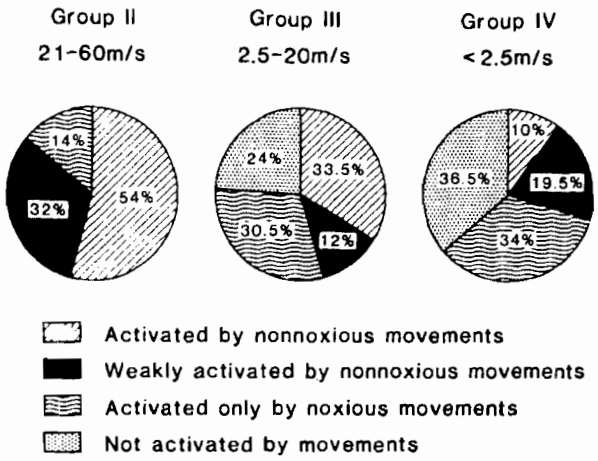

Fig. 3. Proportions of thick myelinated group II units (CVs, > 20 m/sec), thin myelinated group III units (CVs, 2.5–20 m/sec) and unmyelinated group IV units (CVs, < 2.5 m/sec) of the normal joint in the sensitivity classes defined. For all of these units a receptive field was identified in the joint (the graph does not contain mechano-insensitive units).

1983b, 1985; Dorn et al. 1991). The graph contains those units that had detectable receptive fields in the joint. Most fast-conducting group II units (conduction velocities, 20–65 m/sec) with corpuscular endings (Boyd and Davey 1968) were activated by innocuous movements but some were high-threshold units. Within the group III units (conduction velocities, between 2.5 and 20 m/sec) and particularly among the group IV units (conduction velocities, < 2.5 m/sec) a large proportion of fibres was only activated by noxious movements or not activated by movements. A proportion of afferent fibres of the normal joint did not only show responses to mechanical stimuli but they exhibited ongoing discharges in the absence of intentional stimulation. Typically these units were low-threshold units or units which were weakly activated by innocuous movements, and they had low conduction velocites (group III and IV units). By contrast, high-threshold units and mechano-insensitive afferent units had no spontaneous activity (Schaible et al. 1983b; 1985, 1988a).

According to the specificity theory of nociception and pain (see Perl 1984; Willis 1985) the high-threshold fibres (see Fig. 2C) may be considered as nociceptive units since their activation seems to be related to the application of potentially or actually damaging stimuli, e.g., movements against the resistance of the joint structures or intense pressure. Presumably their activation leads to pain sensations (as it has been shown for cutaneous nociceptors) although this has not yet been demonstrated in humans, e.g., by microstimulation of joint nerves. Whether units that are weakly activated by innocuous movements (Fig. 2B) should be considered as nociceptors or as non-nociceptive units is unclear. It should be noted that many low-threshold group III and IV afferents had graded responses to stimuli of innocuous and noxious intensities (see Fig. 2A). Indeed, it has been described before that many thick myelinated group II afferents also show their highest discharge frequencies at the extremes of the movement range although the reports did not specify whether these movements were considered noxious (Burgess and Clark 1969; Clark 1975; Clark and Burgess 1975; Grigg 1975, 1976; Grigg and Greenspan 1977; Ferrell 1980, 1985; Dorn et al. 1991). Nevertheless these low-threshold fibres probably do not convey reliable information to the spinal cord about the innocuous or noxious intensity of a stimulus since their response to an innocuous movement into one particular direction could be stronger than their response to a noxious movement into another direction (Schaible and Schmidt 1983b; Dorn et al. 1991). It is perhaps more appropriate, therefore, that they be classified as proprioceptors.

II.C. Mechanosensitivity of articular afferents in the inflamed joint

Inflammation in a joint is often associated with hyperalgesia (pain during movements in the working range and during application of gentle innocuous pressure) and/or persistent pain (resting pain). Recordings from afferent fibres innervating joints have shown that a majority of the sensory units are 'sensitized' during inflammation and show an increase in their responsiveness to stimuli applied to the joint. This sensitization results in a quantitatively and qualitatively different sensory inflow into the spinal cord and constitutes the peripheral component of articular nociception in inflammation (see also Fig. 1). Changes in the sensitivity of joint afferents have been demonstrated by comparing the response properties of samples of afferents from normal and acutely inflamed knee joints in the cat (Coggeshall et al. 1983; Schaible and Schmidt 1985; Grigg et al. 1986; Dorn et al. 1991) and of samples of joint afferents in normal and chronically inflamed ankle joints in the rat (Guilbaud et al. 1985; Grubb et al. 1991). In the cat the inflammation-evoked changes in the response properties of joint afferents have also been directly documented in long-term recordings of single identified afferents during development of acute inflammation (Schaible and Schmidt 1988a).

II.C.1. Inflammation and group II afferents

During development of inflammation induced by kaolin and carrageenan some group II afferents with corpuscular endings in the knee were shown initially to increase their responses to flexion and other movements of the joint (Schaible and Schmidt 1988a). These mechanoreceptors may, therefore, contribute to the afferent drive of the spinal neurones during movements of the joint in the initial stages of the develop-

ment of inflammation. In later stages (5–15 h after induction of inflammation) the group II afferents in inflamed joints exhibited discharges which were similar to those observed in normal joints (Dorn et al. 1991). Unlike group III and IV fibres (see below) most group II units did not show ongoing activity whether the joint was normal or inflamed.

II.C.2. Sensitization of group III and IV afferents

The majority of the group III and IV afferents have been shown to develop a long-lasting 'sensitization' to mechanical stimuli after the onset of joint inflammation (Coggeshall et al. 1983; Schaible and Schmidt 1985, 1988a; Grigg et al. 1986). Many low-threshold group III and IV afferents were shown to have increased responses to movements in the working range of the joints. This form of sensitization enhances the afferent input to the spinal cord quantitatively. Importantly most high-threshold afferents (Fig. 2C) and those of class 4 (see Fig. 2D) also had reduced thresholds such that they were now activated by movements within the working range of the inflamed joint, e.g., by innocuous flexion and extension. This form of sensitization represents a qualitative change since sensitized high threshold fibres transmit their message 'noxious (and probably painful) movement' to the spinal cord in response to an ordinarily innocuous stimulus. It may be speculated that such a process could render a normal movement in an inflamed joint painful (hyperalgesia in the joint). Sensitization of group III and IV fibres was seen in most cases in the second to third hour after the injection of kaolin and carrageenan into the joint which matches the time course of the development of hyperalgesia which has been observed in awake animals (Schaible and Schmidt 1988a). A lowering of the threshold in group III and IV mechanoreceptors in the rat ankle has also been described in chronic, FCA-induced unilateral inflammation at the ankle (Guilbaud et al. 1985; Grubb et al. 1991). An additional feature of group III and IV fibres in inflamed joints is that many of them have been found to exhibit ongoing discharges when the joint is kept in its resting position. This provides the spinal cord with tonic afferent input which may be the neural basis of resting pain (Schaible and Schmidt 1985, 1988a).

II.C.3. Activation of initially mechano-insensitive afferent fibres

In addition to the sensitization of mechanosensitive afferent fibres another afferent component may be at work during inflammation of the joint. As mentioned above there is also an activation of mechano-insensitive afferent fibres during inflammation. In the MAN and PAN of the normal knee a substantial proportion of unmyelinated fibres and a small proportion of thin myelinated fibres have been identified by electrical stimulation of the axons which were not activated by innocuous or noxious mechanical stimuli applied to the joint (Grigg et al. 1986; Schaible and Schmidt 1988a). In recordings from the PAN units in the sciatic nerve,

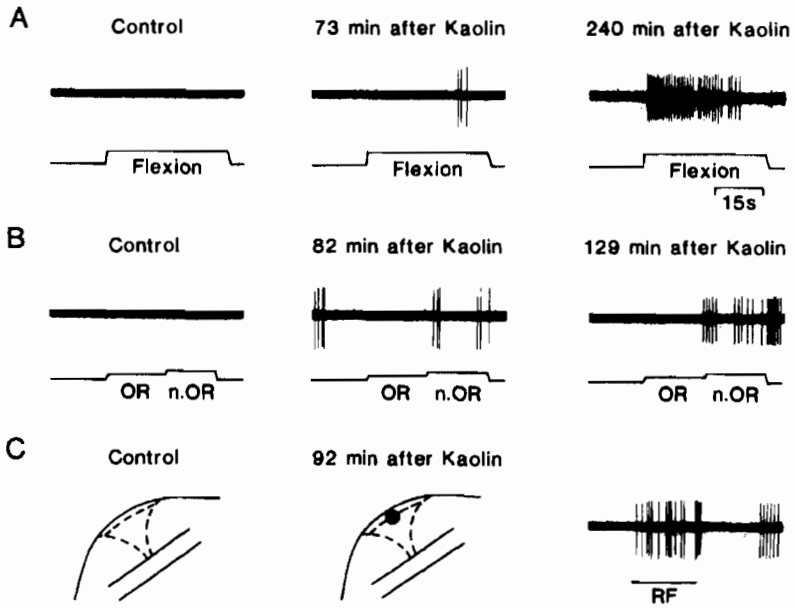

Fig. 4. Induction of mechanosensitivity in an initially mechano-insensitive group IV unit during development of an acute inflammation induced by the intra-articular injections of kaolin and carrageenan. A: responses to flexion of the joint (innocuous movement). B: responses to innocuous outward rotation (OR) and noxious outward rotation (n.OR). C: receptive field of the unit. The specimen on the right shows the response of the unit to stimulation of the receptive field that was detected when the joint was becoming inflamed. (Reproduced from H.-G. Schaible and R.F. Schmidt, J. Neurophysiol., 60 (1988a) 2180–2195, with permission from The American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814.)

only 3 of 41 unmyelinated units and 12 of 18 thin myelinated fibres had a detectable receptive field in the posterior capsule. In the MAN 14 of 38 unmyelinated units and 2 of 24 thin myelinated units were mechano-insensitive but responded to KCl (see below) (Schaible and Schmidt 1988a).

Although many of these mechano-insensitive units are certainly efferent fibres (note the large number of postganglionic efferent units in the joint nerves, Section II.A) several observations have led to the proposal that a proportion of mechano-insensitive fibres are 'silent nociceptors' that become mechanosensitive following the development of inflammatory lesions. These are (1) some mechano-insensitive units were activated by the intra-arterial injections of bradykinin and/or prostaglandin E_2 (Neugebauer et al. 1989). These properties are also shared by a large proportion of afferent fibres with detectable receptive fields and movement sensitivity; (2) mechano-insensitive units in the PAN were also identified in the dorsal roots which contain only afferent fibres (Grigg et al. 1986); and, most importantly, (3) a proportion of mechano-insensitive afferents developed responsiveness to mechanical stimuli and developed some ongoing activity after induction of acute inflammation. The latter feature has been directly observed in MAN units when continuous recordings were made from initially mechano-insensitive fibres during the development of arthritis (Schaible and Schmidt 1988a). An example of such a unit is shown in Fig. 4. In the period prior to inflammation this unit was excited by the electrical stimulation of the MAN and by the intra-arterial injection of KCl but not by local mechanical stimulation and innocuous and noxious movements. In the course of the arthritis the unit showed a receptive field in the patellar region and responses to movements of the inflamed joint.

A lack of mechanosensitivity could be also explained by inaccessibility of the receptive field to local probing. This explanation is unlikely to be the only one since receptive fields sensitive to mechanical probing became apparent during development of inflammation (see Fig. 4). It is possible that mechano-insensitive afferents require some form of sensitization before mechanical stimuli evoke excitation. These units seem, therefore, to be a population of 'silent nociceptors' which are excited only under certain conditions, e.g., inflammation. A note of caution is necessary, however, since some mechano-insensitive units in the joints could not be activated at all during the first few hours of inflammation and it is possible that not all mechano-insensitive afferents are 'silent nociceptors'. The activation and sensitization of mechano-insensitive afferents by inflammatory stimuli such as application of inflammatory mediators or mustard oil and the sensitization of initially unresponsive fibres by noxious stimuli has also been demonstrated for cutaneous afferent fibres (Handwerker et al. 1990; Meyer et al. 1991; Kress et al. 1992) and afferent fibres from viscera (Häbler et al. 1988).

It is difficult to make a good estimate of the proportion of mechano-insensitive afferents within the whole population of joint afferents since it could differ from region to region. A rough estimate would be that in cat knee about one third of the unmyelinated group IV afferents and a small percentage of the group III units from a normal joint do not respond to innocuous and noxious mechanical stimuli under normal conditions. Grigg (1976) and Clark (1975) also described a large population of mechano-insensitive group II fibres but Dorn et al. (1991) were unable to confirm this and found that most group II fibres in the MAN were mechanosensitive and had even low thresholds (see Fig. 3). The precise role of newly recruited nociceptive units is not clear. They could increase the afferent drive of spinal neurones providing, by their recruitment, spatial and temporal facilitation. Alternatively their central effects may be qualitatively different from those exerted by low- and high-threshold afferents, i.e. through different patterns of connectivity.

In summary there is a significant change in the afferent inflow to the spinal cord in the course of joint inflammation. The major effects of inflammation on the afferent fibres are an enhancement of the responsiveness to mechanical stimuli applied to the joint and an induction and/or increase in the continuous ongoing discharges in some fibre groups. Under inflammatory conditions gentle, i.e. normally innocuous movements of the joint lead to increased responses in low-threshold afferent units and to activation of sensitized high-threshold fibres which under normal conditions respond only to noxious stimuli, i.e., movements exceeding the normal working range. In addition, units which are insensitive to innocuous and noxious mechanical stimuli under normal conditions may become mechanosensitive in the course of inflammation. Presumably all of these changes contribute to the mechanical hyperalgesia of the joint (pain during movements in the working range) although the specific contribution of each group of fibres to this phenomenon remains to be determined. The latter reservation has to be made since the activation of afferent fibres may elicit a whole cascade of events in the spinal cord which may influence the spinal processing (see Section III). The increased ongoing sensory inflow into the spinal cord under resting conditions may be related to resting pain.

II.D. Mechanisms underlying alterations in mechanosensitivity

According to our current understanding changes in the sensitivity of afferent fibres constitute the afferent

basis of hyperalgesia and pain in the inflamed joint. It is of great therapeutic interest, therefore, to elucidate the mechanisms leading to sensitization since inhibition or abolition of the sensitizing processes may provide measures to treat pain in the inflamed joint. In this respect it is probably important that most group III and IV afferents are not only sensitive to mechanical but also to various chemical stimuli such as inflammatory mediators. Changes in the mechanical sensitivity of joint receptors arising from joint inflammation may therefore involve several processes (see Fig. 1). There are changes in the physical condition of the joint tissues (synovial effusions, oedema) such that the joint tissues and thus the receptive endings of afferent fibres are possibly under increased physical stresses. There is also a marked change in the chemical milieu after the onset of an inflammatory episode since a number of mediators are released or synthetized. These factors produce not only the inflammatory response but also exert some effects on afferent fibres. Whilst these extraneuronal changes represent stimuli to the receptive endings there may be also changes in the terminal sites themselves that contribute to the increased mechanosensitivity. The following paragraphs will describe factors which may be involved in the neuronal changes observed in afferents from inflamed joints.

II.D.1. Physical changes in joint tissues during arthritis

II.D.1.a. Intra-articular pressure. Under normal conditions fluid cannot readily be removed from joint cavities of human knee joints (Jayson and Dixon 1970a). Indeed small subatmospheric (−12 to 0 mm Hg) or near zero pressures have been recorded in the articular space in both human (Reeves 1966; Jayson and Dixon 1970a; Myers and Palmer 1972) and animal experiments (Reeves 1966; Levick 1979; Shira 1984; Wood and Ferrell 1985). Synovial pressure is normally lowest when joints are in a rested position (angle approx. 90–150°) but rises often becoming positive during flexion (angle approx. 60°) (Levick 1979; Ferrell et al. 1986). Infusions of liquid paraffin (which is not absorbed through the synovial lining) into the joint increase intra-articular pressure in the dog, particularly during flexion and whole nerve recordings from the MAN in these animals have revealed changes in the discharge patterns during joint inflation (Ferrell et al. 1986). In normal joints maximal nerve discharges were observed at extension with a smaller peak at flexion. Lowest discharge rates were observed when the joint was in mid-position. Following inflation of the joint, however, the maximal nerve discharge rate was observed at flexion with little change at extension when compared to the control joint (except in very distended joints). Since whole nerve recordings probably discriminate mainly the larger group II axons it is not yet clear how these stimuli might affect the discharge pattern in group III and IV fibres. The injection of the inflammatory compounds kaolin and carrageenan into the joint cavity caused a transient activation of a proportion of the afferent group III and IV fibres but in these experiments the relationship between defined intra-articular pressure or volume and afferent discharges was not systematically studied (Schaible and Schmidt 1988a).

In human joint disease significant volumes of effusate can be aspirated from joints, up to 70 ml in knee joints (Ropes et al. 1940; Ragan 1946; Ropes and Bauer 1953; Caughey and Bywaters 1963; Jayson and Dixon 1970a) and the mean resting synovial pressure is significantly elevated (approx. 19 mm Hg (Jayson and Dixon 1970a)). This increase in articular volume is also accompanied by a decrease in joint compliance in rheumatoid arthritis. The effect of this is that articular pressure increases more in diseased joints than in normal joints for the same volume of fluid present (Jayson and Dixon 1970a). Not surprisingly, therefore, the pressures recorded in knees of patients with rheumatoid arthritis were far higher than those recorded from control subjects during normal walking. It is, however, difficult to know how these disease-induced changes in the physical condition of the joint relate to discharges from the joint afferents. Group III and IV afferents are known to be sensitized to movements during the development of an inflammation and it is possible that effusions may contribute to this along with changes in the chemical milieu in the joint (see below) especially during the stance phase of normal walking when pressure in diseased joints has been shown to be highest (Jayson and Dixon 1970b).

II.D.1.b. Vascular changes. In addition to changes in the gross pathology of the joint in arthritis there are also changes in the microvasculature. An injection of kaolin into the knee joint in rabbits results in an overall increase in blood flow in the joint as measured using the laser Doppler technique (Khoshbaten and Ferrell 1990). It is likely that changes in blood flow are at least in part mediated by the nervous system, i.e., by afferent and efferent fibres in the joint nerves (for details see Section V).

II.D.2. Inflammatory mediators in joint tissues during arthritis

Several inflammatory mediators (prostaglandins, thromboxanes, leukotrienes, kinins, and others) have been identified in synovial fluid. They are either produced by tissues in the joints and/or are released during joint inflammation in both human joint disease and in experimental arthritis. In order to investigate their pathogenic role in the production of the inflammation-evoked discharges, some of these mediators have been administered locally to the joint tissues, e.g., by close intra-arterial injection, and their effects on the

response properties of identified joint afferents have been analysed. The most clear effects of the different inflammatory mediators are a sensitization and/or excitation of afferent units. Sensitization is an enhanced response of an afferent unit to either a mechanical stimulus, e.g., flexion through a fixed angle or pressure applied to the joint, or a chemical stimulus, caused by application (usually by close arterial injection) of a test compound. Excitation is an induction or increase of firing in the afferent fibre following application of a stimulus or a compound.

The application of individual inflammatory mediators has shown their potential action(s) on afferent units. Some inflammatory mediators induced patterns of firing in afferent nerve fibres which are similar to those seen under inflammatory conditions. Furthermore, single-unit recordings have revealed that joint afferents are not homogeneous with regard to their chemosensitivity. Another important factor is that the tissues of the joint and invading cells produce a number of inflammatory mediators which may act independently at the same time or act synergistically whereby the action of one mediator is dependent on the action of another. Possible therapeutic interventions have been attempted, therefore, in experimental animals using antagonists to different inflammatory mediators. The following paragraphs will summarize some of the available data on the actions of inflammatory mediators on nerve fibre activity. The data are, however, incomplete for at least 3 reasons. (1) Only some mediators and antagonists have been studied. (2) The interactions between individual mediators have not been adequately determined. (3) Using methods currently employed it is impossible to study the molecular aspects of the activation and/or sensitization of the receptive endings themselves; related studies have been made, however, in the cell bodies, i.e., the dorsal root ganglion cells (Rang et al. 1991).

II.D.2.a. Prostaglandins. The prostaglandins, PGE_1, PGE_2 (or its breakdown product, PGB_1), PGI_2 (or its breakdown product, 6-keto-$F_{1\alpha}$), $PGF_{2\alpha}$ and PGD_2 have all been identified either in synovial effusions from patients with a variety of inflammatory joint diseases or are produced in increased amounts by cultured synovial cells isolated from patients with rheumatoid arthritis (Robinson and Levine 1973; Dayer et al. 1976; Trang et al. 1977; Sturge et al. 1978; Egg et al. 1980; Brodie et al. 1980; Bombardieri et al. 1981; Tokunaga et al. 1981; McGuire et al. 1982; Salmon et al. 1983; Egg 1984; Moilanen 1989). In most cases the concentrations of each of these prostaglandins is raised in diseased joints in man although there is considerable variation between individual studies probably due to the different assay techniques used. In experimental models of joint inflammation (e.g., carrageenan-induced arthritis, urate crystal-induced arthritis, FCA-induced arthritis or salmonella-induced arthritis), PGE_1, PGE_2 (or PGB_1), PGI_2 (or 6-keto-$F_{1\alpha}$) and $PGF_{2\alpha}$ have also been measured in higher than normal concentrations in synovial fluid or joint tissues in a variety of species (see for example: Blackham et al. 1974; Glatt et al. 1974; Moncada et al. 1975; Arai and Aizawa 1978; Parnham et al. 1978; Ahnfelt-Ronne et al. 1980; Wada et al. 1984). Similarities may exist, therefore, between the commonly used models of joint inflammation in animals and human arthritic disease with respect to the inflammatory mediators present. PGE_2 and PGI_2 seem to be particularly important mediators of inflammatory joint disease due to the fact that they are present in high concentrations in inflamed tissue compared to other prostaglandins.

The success of prostaglandin synthesis inhibitors, e.g., salicylic acid derivatives, indomethacin, etc., as analgesic drugs is strongly correlated with their ability to reduce prostaglandin production in both human joint disease (Robinson and Levine 1973; Dayer et al. 1976; Trang et al. 1977; Sturge et al. 1978; Egg et al. 1980; Brodie et al. 1980; Tokunaga et al. 1981; McGuire et al. 1982; Egg 1984) and in experimentally induced arthritis (Van Arman et al. 1970; Blackham et al. 1974; Moncada et al. 1975; Arai and Aizawa 1978; Ferreira et al. 1978; Wada et al. 1984). Whilst PGE_2 and PGI_2 have actions on joint tissues, e.g., on synovial microcirculation (Dick and Grennan 1976), they are also involved in the excitation and/or sensitization of joint afferents. In behavioural experiments, for example, PGE_1, PGE_2 and PGI_2 have been shown to incapacitate conscious dogs when injected into the knee joint (Rosenthale et al. 1972; Ferreira et al. 1978). Interestingly the onset of the effect of PGE_2 was slower than that of PGI_2 and also outlasted it presumably due to the different stabilities of these two compounds (Granström and Kumlin 1987; Roberts 1987). In electrophysiological studies non-steroidal anti-inflammatory drugs (NSAID) have been found to reduce both spontaneous and mechanically evoked activity (either flexion of the knee or pressure applied by a mechanical indenter) in group III and IV fibres in both acute (Heppelmann et al. 1986) and chronic models of joint inflammation (Guilbaud and Iggo 1985; Grubb et al. 1991) in the cat and rat, respectively. The reductions in spontaneous or mechanically evoked activity were seen within 10–20 min of application of salicylic acid derivatives and indomethacin in both rat and cat (Guilbaud and Iggo 1985; Heppelmann et al. 1986; Grubb et al. 1991) and in the rat recovery from lysine acetylsalicylate (an aspirin analogue) occurred within 1–2 h (Guilbaud and Iggo 1985). Cats lack the enzyme glucuronyl transferase and cannot readily metabolize salicylic acid derivatives (Davis and Donnally 1968; Davis and Westfall 1972) and this may explain why the effects of acetylsalicylic acid on resting and mechanically

evoked discharges in group III and IV fibres of cat knee did not recover (Heppelmann et al. 1986). Whilst it is generally thought that salicylic acid analogues act by inhibiting prostaglandin synthesis, there is some evidence that they may also have other actions which could account for their effects on the firing of afferent fibres (Brune et al. 1991). In addition to their peripheral actions the central effects of aspirin and other NSAIDs must also be taken into account (Carlsson et al. 1988; Taiwo and Levine 1988; McCormack and Brune 1991; Jurna et al. 1992; Malmberg and Yaksh 1992a, b).

In an attempt to determine the prostaglandins responsible for the NSAID-sensitive component of the sensitization of joint afferents, PGE_2 was subsequently administered to the inflamed knee joint in the cat and rapidly reversed the inhibitory effects of both indomethacin and acetylsalicylic acid on group III and IV afferents in a dose-dependent manner (Heppelmann et al. 1986). In rats with FCA-induced monoarthritis PGE_2 did not reverse the effects of lysine acetylsalicylic acid on spontaneous or mechanically evoked activity in group III and IV fibres (Grubb et al. 1991). The reasons for these differences are unclear and it is not certain, therefore, whether the effects of acetylsalicylic acid or indomethacin are purely a result of the inhibition of PGE_2 synthesis or whether other products of the arachidonic acid metabolism might be involved in the sensitization of joint afferents. Indeed PGI_2 can sensitize and excite group III and IV afferents in normal cats (Schepelmann et al. 1992) and normal rats (Birrell et al. 1991).

PGE_1 (Heppelmann et al. 1985) and PGE_2 (Heppelmann et al. 1985; Schaible and Schmidt 1988b) administered intra-arterially to the normal knee joint were shown to excite and sensitize some group III and IV articular units. About 60% of the group III and IV units in the cat MAN could be excited by PGE_2 (amounts of 0.03–30 μg) and 64% and 25% of group III and IV units, respectively, were found to be sensitized to movements. The excitatory effects started approximately 30 sec after close arterial injection of PGE_2 and recovery was typically seen within 4 min but some fibres continued to discharge at an enhanced rate throughout the recording period (Schaible and Schmidt 1988b). The sensitizing effect was generally seen within 1–2 min after close arterial injection of PGE_2 and lasted for some time (> 10 min). Excitation was seen in both low and high mechanical threshold group III and IV fibres. Interestingly the sensitizing effect to mechanical stimulation was observed in low and high threshold group III units but only, however, in those group IV units that had low thresholds and not in those with high thresholds.

By contrast, only 18% of joint mechanoreceptors (filaments with group III and IV fibres) in the rat ankle joint were excited by PGE_2 and only 20% were sensitized to movements (Grubb et al. 1991). In those fibres which were sensitized or excited by PGE_2 the onset of the response was slow starting approximately 5 min after arterial injection and lasted 10–15 min. The reason for the difference in the proportions of fibres excited by PGE_2 in cat and rat joints is unclear but both PGI_2 and cicaprost, a more stable and potent agonist at the type-I prostaglandin receptor (IP receptor) were found to excite the majority (PGI_2 = 80%, cicaprost = 92%) of group III and IV mechanoreceptors in the rat. In addition, both PGI_2 (80%) and cicaprost (88%) sensitized ankle joint receptors to repeated graded stimulation applied using a mechanical indenter. These results suggest that PGI_2 may play a more important role than PGE_2 in the modulation of mechanoreceptor activity in this species (Birrell et al. 1991).

Since prostaglandins induce similar neuronal changes to those seen in models of experimental inflammation (ongoing activity, sensitization to movements) they should be considered as important mediators involved in the pathogenesis of inflammation-evoked discharges. The data clearly show, however, that only proportions of articular afferents are affected by prostaglandins and that some changes (sensitization of high-threshold group IV afferents for mechanical stimuli) cannot be produced by the prostaglandins which have been tested to date. It may be asked, therefore, whether failure of NSAIDs in pain treatment results in part from the possibility that in many units other mediators than prostaglandins might be involved in the activation and/or sensitization.

II.D.2.b. Bradykinin. This kinin is a potent algesic substance and it has been shown to excite and/or sensitize afferent fibres innervating skin, muscle, joint and viscera (see refs. in Kanaka et al. 1985; Neugebauer et al. 1989; Meller and Gebhart 1992; Mizumura et al. 1992). Bradykinin has been identified in synovial effusions in human joint disease (Melmon et al. 1967; Hargreaves et al. 1988) and in a model of acute paw inflammation (Hargreaves et al. 1988). Local increases of bradykinin in inflamed tissue have recently been demonstrated in patients after oral surgery and in rats during carrageenan-induced inflammation of the hindpaw using microdialysis probes (Hargreaves and Costello 1990). The application of bradykinin to the joint was found to be a powerful stimulus for afferent units. Intra-arterial bolus injections of bradykinin in amounts of 0.026–26 μg close to the joint excited the vast majority of the group III and IV afferents in the MAN of cat knee (Kanaka et al. 1985) whilst in the rat similar doses (0.1–10 μg) excited approximately one-half of the units supplying the ankle (Grubb et al. 1991). The excitatory effect of bradykinin started 10–20 sec after close arterial injection and usually lasted

between 30 and 60 sec. Repeated application of bradykinin resulted in a pronounced tachyphylaxis. Bradykinin also sensitized 70% and 44% of the group III and IV units in the cat and rat, respectively, to movements (Neugebauer et al. 1989; Grubb et al. 1991). This sensitization included a lowering of threshold in high-threshold group III and IV units (to become responsive to innocuous movements) or the induction of mechanosensitivity in initially mechano-insensitive afferents (Neugebauer et al. 1989). The duration of the sensitizing action of bradykinin to mechanical stimuli was variable. In some units sensitization appeared to be long-lasting whereas in others it lasted only few minutes but in all cases it was longer than the excitatory effect (Neugebauer et al. 1989).

Bradykinin sensitivity (excitation or sensitization) in group III and IV does not seem to be related to the mechanical threshold of fibres since high- and low-threshold fibres (and some initially mechano-insensitive afferents) appeared to be affected (Kanaka et al. 1985; Neugebauer et al. 1989). By contrast bradykinin rarely excited low-threshold group II mechanoreceptors in the knee joint of the cat (Kanaka et al. 1985). In summary bradykinin exerts its effects on articular group III and IV units and induces afferent fibre activity which is qualitatively similar to that seen in experimentally induced joint inflammation suggesting that bradykinin might be an important mediator. Due to the short duration of the effect and the tachyphylaxis of the response, however, additional mediators or factors seem to be required to produce the full effect of inflammation. The effect of bradykinin antagonists on the discharges of articular afferents has still to be determined. Inhibitory effects may be expected since in human blister base experiments B_2 receptor antagonists reduced the algesic effect of bradykinin whilst B_1 receptor antagonists were ineffective (Whalley et al. 1987). Similarly, co-administration of a bradykinin antagonist together with carrageenan into the rat hindpaw suppressed hyperalgesia, hyperthermia and oedema which are usually observed after carrageenan alone (Costello and Hargreaves 1989).

Interactions between bradykinin and prostaglandins have also been studied. Both PGE_1 and PGE_2 have been shown to enhance the reflex rise in blood pressure produced by injecting bradykinin into the joint cavity (Moncada et al. 1975). In experiments where direct recordings were made from articular afferents PGE_2 was shown to enhance the excitatory effects of bradykinin in 50% of group III fibres and in 75% of group IV fibres in the MAN of cat knee (Schaible and Schmidt 1988b) and 90% of fibres (mixed group III and IV fibres) in the rat ankle (Grubb et al. 1991). In about 50% of the cat knee joint afferents (low and high threshold) and in some initially mechano-insensitive afferents the combined application of PGE_2 and bradykinin was found to have stronger sensitizing effects on the responses to movements (change of threshold or size of response) than bradykinin or PGE_2 alone. These findings demonstrate the power of the combination of inflammatory compounds. The interactions of bradykinin with PGI_2 were similar to that with PGE_2 (Schepelmann et al. 1992).

II.D.2.c. Serotonin. Serotonin (5-HT) was a potent excitant of approximately two-thirds of group III and IV mechanoreceptors in the ankle joint of normal and arthritic rats (Birrell et al. 1990). The response to 5-HT consisted of at least two components, a rapid transient excitatory component which was particularly prone to tachyphylaxis and a delayed excitation which started after 15–30 sec and lasted for up to 5 min. The initial transient burst seemed to be inhibited by 5-HT_3 receptor antagonists, e.g., GR38032F whilst delayed excitation was inhibited by 5-HT_2 receptor antagonists, e.g., ketanserin. In the cat group III (43%) and group IV fibres (73%) of the MAN of the knee joint were excited by 5-HT and in the group III fibres (not in the group IV fibres) this excitatory effect was more pronounced (longer duration, less tachyphylaxis) when the joint was inflamed (Herbert and Schmidt 1992).

Spontaneous activity, a marked characteristic of sensitized articular afferents in arthritic joints was reduced by both 5-HT_2 and 5-HT_3 antagonists in fibres supplying the rat ankle joint indicating that 5-HT may be involved in the sensitization of mechanoreceptors in adjuvant-induced monoarthritis (Birrell et al. 1990). In the MAN of the inflamed knee joint of the cat 5-HT sensitized a proportion of group III and IV units to movements for short periods (Herbert and Schmidt 1992).

II.D.2.d. Other inflammatory mediators. There are substantial numbers of arachidonic acid metabolites (prostaglandins, leukotrienes and thromboxanes) and peptides which have not yet been properly investigated for their actions on articular afferents. The concentrations of the leukotrienes, e.g., LTB_4, LTC_4, LTD_4 and LTE_4 are all increased in synovial fluid from patients with inflammatory joint diseases (Klickstein et al. 1980; Rae et al. 1982; Davidson et al. 1983; Koshihara et al. 1988; Quinn 1990) and in synovial effusions obtained from animals with experimentally induced arthritides (Carlson et al. 1986; Herlin et al. 1988; Fogh et al. 1989). Whilst the synthesis of leukotrienes has been correlated with the severity of the inflammatory lesion, e.g., 15-HETE, an inhibitor of LTB_4 synthesis has been found to decrease clinical symptoms of inflammation in dog knee joints (Herlin et al. 1990). No electrophysiological studies have yet been made with this or other related compounds which are known to be present in increased amounts in inflamed joint tissue, e.g., thromboxane B_2 (Trang et al. 1977; Brodie et al. 1980; Bomardieri et al. 1981; Salmon et al. 1983; Egg 1984),

to determine whether they can affect the activity or sensitivity of articular afferents. In rat skin, however, there is some evidence that some group III and IV mechanoreceptors are sensitized to mechanical stimuli by LTB_4 (Martin et al. 1987).

II.D.3. Inhibitory influences on joint afferents

Whilst joint afferents are excited and sensitized by inflammatory mediators their activity may be inhibited by other compounds. The reduction of activity by non-steroidal analgesics has already been described in the last section. Inhibition by capsaicin and opioid peptides has also been reported.

II.D.3.a. Capsaicin. This compound is a naturally occurring constituent of hot red peppers and is known to have both neuroexcitatory (Baranowski et al. 1986; Szolcsanyi 1987; Wood et al. 1988; He et al. 1990; Rang et al. 1991) and neurotoxic effects (Buck and Burks 1986; Rang et al. 1991). Capsaicin activated polymodal group IV fibre nociceptors and in the joint the situation seems to be similar. Close arterial injections of capsaicin (10^{-4} to 10^{-6} M) were shown to induce a brief discharge in both group III and IV afferents. This was accompanied by a rapid loss of mechanosensitivity of the afferents and a loss of sensitivity to chemical stimulation by bradykinin. In some cases recovery was seen within a few minutes. Excitation and desensitization by bradykinin were mainly found in 'nociceptive' group III and IV fibres having high thresholds or not being activated by movements but not in those having low thresholds (He et al. 1990). The mechanisms underlying these desensitizing effects are not yet clear. It is possible that the application of capsaicin may be successfully used for treatment of arthritic pain. It was reported that the administration of a capsaicin cream to painful knees in patients suffering from rheumatoid arthritis or osteoarthritis produced more pain relief than a placebo control (Deal et al. 1991). The relationship of this effect to the activity in sensitized joint afferents remains to be clarified.

II.D.3.b. Opioid peptides. Several lines of evidence suggest that afferent fibres including joint afferents may be equipped with opioid receptors. (1) Several behavioural studies have shown that opioid receptor agonists acting at peripheral opioid receptors can produce antinociception under inflammatory conditions (Ferreira and Nakamura 1979; Joris et al. 1987; Stein et al. 1988, 1989). Stein et al. (1988), for example, showed that intraplantar fentanyl (a mu-receptor agonist) reversed paw hyperalgesia in a naloxone-reversible manner in rats with unilateral inflammation induced with FCA. (2) Russell et al. (1987) recorded the activity from single afferent fibres in MAN of cat knee joint after induction of joint inflammation with kaolin/carrageenan. Ongoing activity in most group III and IV fibres was reduced in a naloxone-reversible manner by kappa-receptor agonists (U50,488H and ethylketocyclazocine) and/or, to a lesser extent, by mu-receptor agonists. The effects of delta-receptor agonists on afferent discharges have not been studied. (3) Yaksh (1988) has shown that substance P release from primary afferent fibres into the cat knee joint evoked by antidromic nerve stimulation was inhibited by sulfentanil (mu-receptor agonist) and by D-Ala^2, D-Leu^5-enkephalin (DADL, delta-receptor agonist) and D-Pen^2, D-Pen^5-enkephalin (DPDPE, delta-receptor agonists) in a naloxone-reversible manner. Kappa opioid-receptor agonists were without effect in this study. Collectively these results indicate that peripherally acting opioid peptides may interfere with the afferent and the efferent activity of joint afferents although the importance of specific receptor types (mu, delta and kappa) does not seem to be settled.

The potential importance of these findings is suggested in clinical studies in which intra-articular morphine (mu-receptor agonist) produced pain relief following knee arthroscopy without obvious systemic effects (Khoury et al. 1990; Stein et al. 1991). The use of peripherally acting opioids may turn out to be an alternative treatment for joint pain provided that compounds can be synthetized that do not cross the brain–blood barrier and are not limited in their effect by the development of tolerance.

It is an interesting question whether there are endogenous opioids that act on the peripheral terminals of afferent fibres. Using the cold water swim stress (CWS) model to induce the release of endogenous opioid peptides Stein et al. (1990a) have shown that CWS can increase the paw pressure threshold on the inflamed paw but not the unaffected paw in a naloxone-reversible manner in rats with adjuvant-induced monoarthritis. The use of receptor selective antagonists in these studies suggested the involvement of mu- and delta- but not kappa-receptors. Furthermore, i.v. injections of antibodies to β-endorphin but not antibodies against Met-enkephalin or dynorphin abolished the effect of CWS on paw hyperalgesia. Finally, β-endorphin injected into the inflamed paws in these rats was antinociceptive and this effect was reversed by naloxone and selective mu- and delta-receptor antagonists. These observations have led to the conclusion that β-endorphin released by CWS acts to reduce hyperalgesia in the inflamed paw of rats with a monoarthritis.

The origin of these opioid peptides in the periphery is not clear although there is some experimental evidence to suggest that there might be local release from inflammatory cells within the inflamed paw. Indeed, opioid staining was almost absent in the normal tissue whereas intense staining was seen in the inflamed paw where several cell types (macrophages, mast cells and lymphocytes and plasma cells) were immunoreactive

for opioid peptides, e.g., β-endorphin (Stein et al. 1990b). The amount of β-endorphin and Met-enkephalin (but not dynorphin) was significantly increased in the tissues of the inflamed paw of monoarthritic rats. The authors suggest that during inflammation antinociception can be mediated by opioid peptides released locally from immune cells involved in the inflammatory process.

In summary the development of an inflammation in the joint is associated with gross physical changes such as synovial effusion and tissue oedema and with the local release and/or synthesis of inflammatory mediators which may contribute to these changes. Recordings from joint afferents have shown that the application of some inflammatory mediators (PGE_2 and PGI_2, bradykinin and 5-HT) leads to excitation and/or sensitization to mechanical stimuli in group III and IV afferent fibres in the joint nerves. These data suggest that these mediators play a role in the generation of hyperalgesia and/or pain associated with inflammation. It should be noted, however, that only proportions of the afferent fibres were affected by the particular compounds and that not all the infammatory mediators have been studied in regard to their excitatory and/or sensitizing effect on articular units. Furthermore the effects of receptor antagonists for identified inflammatory mediators should be studied in order to demonstrate the involvement of these mediators in the inflammation-evoked discharges in joint afferents in different types and at different stages of inflammation. Prostaglandins may enhance the effects of bradykinin and this example suggests that the discharges in units from inflamed joints may depend on the actual 'mixture' of inflammatory mediators rather than on individual mediators. The latter point, however, is difficult to evaluate at the moment since the studies on the presence and concentrations of inflammatory mediators are usually focussed on few substances. The inflammation-evoked discharges in articular afferents can be reduced in some cases by non-steroidal analgesic drugs thus

TABLE I

NEUROPEPTIDES IN ARTICULAR AFFERENTS

Peptide and structure in which the peptide was identified	Species	Reference
Substance P		
dorsal root ganglion cells of knee joint afferents	rat	O'Brien et al. (1989)
dorsal root ganglion cells of knee joint afferents	cat	Hanesch et al. (1991)
fibres with varicose endings in synovial tissue of knee	rat	Bjurholm et al. (1990)
nerve fibres in synovium of normal and inflamed (FCA) ankle joints	rat	Konttinen et al. (1990) Hukkanen et al. (1991)
fibres in vertebral body, intervertebral discs, ligaments	rat	Ahmed et al. (1991)
fibres in lumbar facet joint capsule and supraspinous ligament	rabbit	El-Bohy et al. (1988)
fibres in temporomandibular joint soft tissue	monkey	Johansson et al. (1986)
nerve fibres in synovial folds of lumbosacral zygapophyseal joints	human	Giles and Harvey (1987)
nerve varicosities in plical synovial tissue in facet joints	human	Grönblad et al. (1991)
fibres in synovium	human	Pereira da Silva and Carmo-Fonseca (1990)
nerve fibres in synovial tissue of knee joint	human	Grönblad et al. (1988)
Neurokinin A		
dorsal root ganglion cells of articular afferents	cat	Hanesch et al. (1992)
Calcitonin gene-related peptide		
dorsal root ganglion cells of articular afferents	rat	O'Brien et al. (1989)
dorsal root ganglion cells of articular afferents	cat	Hanesch et al. (1991)
fibres with varicose endings in synovial tissue of knee	rat	Bjurholm et al. (1990)
fibres in temporomandibular disk	rat	Ichikawa et al. (1989)
fibres of joint capsules	rat	Kruger et al. (1989)
fibres in vertebral body, intervertebral discs, ligaments	rat	Ahmed et al. (1991)
nerve fibres in synovium of normal and inflamed (FCA) ankles	rat	Konttinen et al. (1990)
fibres in synovium	human	Pereira da Silva and Carmo-Fonseca (1990)
nerve fibres in synovial tissue of knee joint	human	Grönblad et al. (1988)
Galanin		
nerve varicosities in plical synovial tissue in facet joints	human	Grönblad et al. (1991)
Met-enkephalin		
nerve fibres in synovial tissue of knee joint	human	Grönblad et al. (1988)
Leu-enkephalin		
nerve fibres in synovial tissue of knee joint	human	Grönblad et al. (1988)
Neuropeptide Y		
fibres adjacent to and within blood vessels	rat	Bjurholm et al. (1990)
perivascular fibres in synovial tissue	human	Mapp et al. (1990)
fibres in synovium	human	Pereira da Silva and Carmo-Fonseca (1990)

explaining, at least in part, the analgesic actions of these compounds in man. Recently inhibitory actions on joint afferents have also been described for capsaicin and opioids and these compounds may be added in the future to the repertoire of analgesics used for the therapy of joint pain.

II.E. Neuropeptides in joint afferents and neurogenic inflammation

II.E.1. Peptidergic innervation of joints

As in other peripheral nerves (see Duggan and Weihe 1991) a proportion of the afferents in joint nerves of several species including humans contain particular peptides (Table I). Some neuropeptides are thought to be involved in neurogenic mechanisms of inflammation since they produce vasodilatation and plasma extravasation in the innervated tissue (Holzer 1988). Neuropeptides in joint afferents could therefore be important in the pathophysiology of inflammatory diseases in the joint, either in the joint itself (as factors contributing to inflammatory processes) or in the spinal cord (as factors modifying the process of signal transmission, see Section III). The involvement of certain neuropeptides in the pathology of joint lesions is also supported indirectly by the observation that the synthesis of these peptides is enhanced during arthritis (see Section III). It is not clear at the moment, whether neuropeptides in joint afferents also have physiological functions under normal conditions.

In order to identify the proportion of joint afferents containing particular neuropeptides, the dorsal root ganglion cells of knee joint afferents have been labelled with Fast Blue (this marker is retrogradely transported) and treated with antisera to several neuropeptides. In a study in the rat (O'Brien et al. 1989) Fast Blue was injected into the knee joint cavity and sections of labelled neurones were subsequently treated with antineurofilament antibody RT97 which labels large light cells with myelinated axons but not small dark cells with unmyelinated axons (Lawson et al. 1984). Calcitonin gene-related peptide-like immunoreactivity (CGRP-li) was identified in 7 of 9 (78%) RT97-negative (small dark) cells and in 37 of 53 (70%) RT97-positive (large light) cells. Substance P-li (SP-li) was contained in 12 of 18 (66%) RT97-negative and in 10 of 59 (17%) RT97-positive neurones. None of the labelled neurones contained somatostatin-li (SOM-li). Somewhat different results were obtained for nerve fibres innervating the cat knee joint (Hanesch et al. 1991). In these experiments the MAN and the PAN were cut and Fast Blue was taken up by the cut nerve ends. Of the Fast Blue-labelled DRG cells from joint afferents (2783 altogether) about 16–17% contained SP-li, and about 32–35% showed CGRP-li. SP-li was found in the DRG cells with the smallest diameters whereas CGRP-li was identified in small as well as in medium-sized somata. Neurokinin A-li (NKA-li) was found in about 4.5% of the MAN afferents (Hanesch et al. 1992) The coexistence of neuropeptides in articular afferents has not been investigated in detail. It is also not known whether all joint afferents contain peptides or whether a proportion is non-peptidergic. Furthermore it is not clear whether there is a relationship between the response properties of an afferent fibre in the joint nerve and the peptides that are contained in the soma and terminals of the neurone.

Studies on the distribution of peptide containing nerve fibres in the different tissue layers of animal and human joints are also summarized in Table I. In humans the analysis was done either on material from patients who underwent operations or from materials collected postmortem. Due to obvious difficulties these studies provide only examples of peptidergic fibres in articular tissues rather than a complete analysis of the peptidergic innervation. In addition, it has not been possible to clearly identify fibres as afferent or efferent since the location of the cell bodies could not be determined. Several reports agree on the presence of SP-li (Johansson et al. 1986; Giles and Harvey 1987; El-Bohy et al. 1988; Grönblad et al. 1988, 1991; Bjurholm et al. 1990; Pereira da Silva and Carmo-Fonseca 1990; Mapp et al. 1990; Ahmed et al. 1991) and CGRP-li (Grönblad et al. 1988; Bjurholm et al. 1990; Ichikawa et al. 1989; Kruger et al. 1989; Pereira da Silva and Carmo-Fonseca 1990; Mapp et al. 1990; Ahmed et al. 1991) in nerve fibres of different animal and human joints. Fibres containing these peptides were considered as afferent and, interestingly, they were also described in the synovial layer where the presence of free nerve endings has been disputed in histological studies (see Section II.A). Nerve fibres with neuropeptide Y-li (NPY-li) were predominantly found adjacent to and within blood vessels. The presence of other peptides in nerve fibres supplying joints has not been as comprehensively studied. Attempts to localize nerve fibres immunoreactive for SOM, vasoactive intestinal polypeptide (VIP), bombesin and Leu-, Met-enkephalin have proved negative (Pereira da Silva and Carmo-Fonseca 1990) or positive (see Table I).

II.E.2. Release and effects of neuropeptides

The electrical stimulation of C fibres in PAN innervating the cat's knee joint evoked plasma extravasation in the joint and this plasma extravasation was reduced by application of neurokinin (NK) receptor antagonists (Ferrell and Russell 1985). This suggests that tachykinins are released from nerve fibres, and indeed release of immunoreactive SP (ir-SP) into the knee joint has been demonstrated during electrical stimulation of unmyelinated fibres in the sciatic nerve (Yaksh 1988). The release of other neuropeptides has not, however,

been directly demonstrated. It appears that SP has effects on the articular vasculature and on cells involved in the inflammatory response. Injections of SP into the synovial cavity of rat knee joints were shown to evoke plasma extravasation (Lam and Ferrell 1989a,b, 1990). In addition to the presumed direct actions of SP on blood vessels there seems to be another component arising from an indirect effect involving mast cells. Indeed pretreatment with H_1 and H_2 receptor antagonists and with methysergide (a 5-HT receptor antagonist) had partially inhibited a SP-induced inflammatory response in rat knee joints (Lam and Ferrell 1990).

Attempts to identify the NK receptor sub-type responsible for these actions of SP have shown that the specific NK_1 receptor agonist (Sar^9, $Met(O_2)^{11}$)-SP mimicked well the extravasation caused by SP whereas the specific NK_2 receptor agonist (Nle^{10})-NKA_{4-10} had only some effect at high concentration and the specific NK_3 receptor agonist ($MePhe^7$)-neurokinin B (NKB) had no effect (Lam and Ferrell 1991). These results suggest that NK_1 receptors and the endogenous NK_1 receptor agonist SP are mainly responsible for the neurogenic extravasation in the knee (Lam and Ferrell 1991). Indeed the other tachykinins, NKA and NKB caused no (NKA) or less plasma extravasation than SP (NKB) when injected into the rat knee joint (Lam and Ferrell 1991). This is displayed in Fig. 5 which shows the effects evoked by single tachykinins and those evoked by co-administration of peptides. NKA by itself produced no response but it caused a significant increase of the effect of SP (Fig. 5B). NKB in a high dose caused extravasation by itself but did not affect the SP-induced plasma extravasation (Fig. 5C). The specific NK_1 receptor agonist caused plasma extravasation by itself and increased the effect evoked by SP (Fig. 5D). In the same study the injection of CGRP neither caused extravasation nor potentiated the SP effect when co-administered with SP (Fig. 5A) although both peptides have been shown to interact in the vasodilator reaction in the skin (Brain and Williams 1988). A synergistic action of SP and CGRP on plasma extravasation has been described, however, in experiments in which the rat knee joint was co-perfused with SP and CGRP in such low concentrations of the neuropeptides that neither SP nor CGRP alone caused an effect (Green et al. 1992). These different results stress the need to know the local concentrations of neuropeptides in the joint in order to define their pathogenic role in inflammatory joint diseases.

In addition to its vascular effects SP also has other actions in joint. This peptide can, for example, increase the production of prostaglandins in cultured synoviocytes (Lotz et al. 1987) and it had effects on white blood cells. Their various functions have, however, been summarized recently and the reader is referred to these articles (Levine et al. 1987; Holzer 1988). Interestingly there is not much evidence that neuropeptides directly influence the sensory functions of afferent fibres. Substance P elicited either no effect or only weak excitation but no sensitization in cutaneous afferents (Fitzgerald and Lynn 1979; Cohen and Perl 1990) and in testicular afferents (Kumazawa and Mizumura

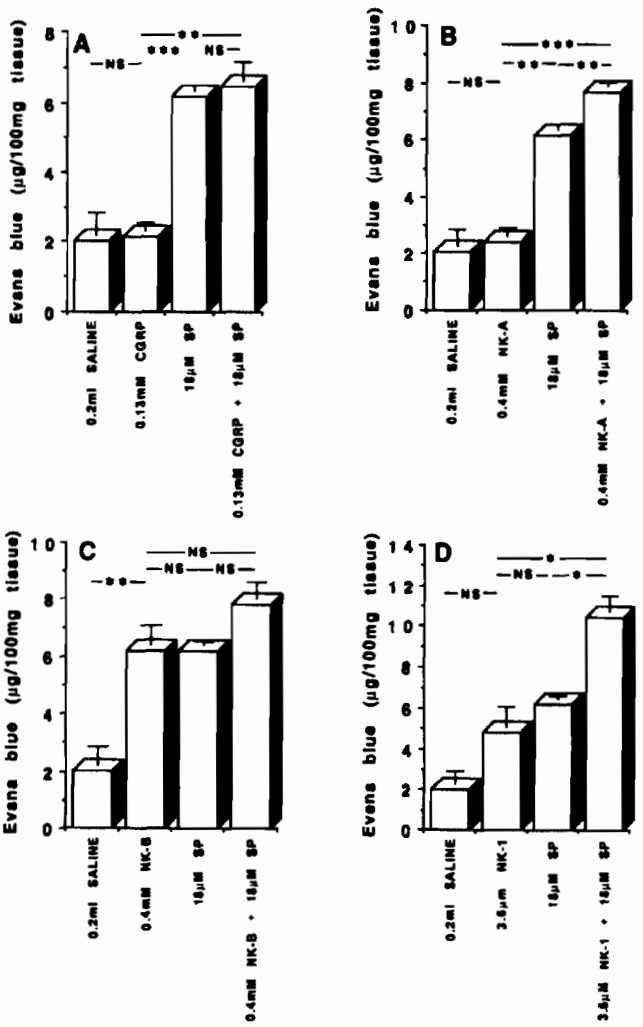

Fig. 5. Effects of co-administration of substance P (SP) with (A) calcitonin gene-related peptide (CGRP), (B) neurokinin A (NKA), (C) neurokinin B (NKB), and (D) specific neurokinin-1 receptor agonist (NK_1) on plasma extravasation into the knee joint capsule of the rat. The neuropeptides were injected into one knee (total volume, 0.2 ml) and saline was injected into the other knee as a control and these compounds were left in the joints for 4 h after which the animals were killed. Evans Blue was injected into the external jugular vein and after killing of the animals Evans Blue was extracted from tissue of the joint and analysed. Evans Blue represents the difference between the test (neuropeptide-injected) and the control (saline-injected) knee for each group of 5 animals. Mean with S.E.M. shown by vertical bars. Significant difference: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, no significant difference. (Reproduced from Lam F.Y. and Ferrell, W.R., Br. J. Pharmacol., 103 (1991) 1263–1267, with the permission from the authors and MacMillan Press Ltd., Scientific and Medical Division, Hampshire, RG21 2XS, UK.)

1979; Mizumura et al. 1987). Neuropeptides may facilitate the excitation of afferent fibres in so far as they may increase the local concentration of inflammatory mediators which then excite or sensitize afferent fibres (see Section II.D). This subject has to be investigated further.

II.E.3. Contribution of neurogenic factors to experimental arthritis

Since some neuropeptides evoke reactions in the tissue that are part of inflammatory responses they may be important in the pathogenesis of arthritis. Indeed, several studies have suggested a contribution of afferent fibres and neuropeptides to the expression of chronic inflammatory lesions in the joint. The inflammatory signs induced by FCA-polyarthritis in the rat were shown to be less severe when the afferent fibre function was impaired by pretreatment of the animal with the neurotoxin capsaicin. This was associated with an attenuation of the inflammation-evoked increase in ir-SP content in sciatic nerve, saphenous nerve, dorsal root ganglia, dorsal roots, and dorsal spinal cord (Colpaert et al. 1983). Fig. 6 shows the increase in the diameter of paws and joints (upper panel) and the decrease of body weight (lower panel) when polyarthritis developed (circles). These symptoms were less se-

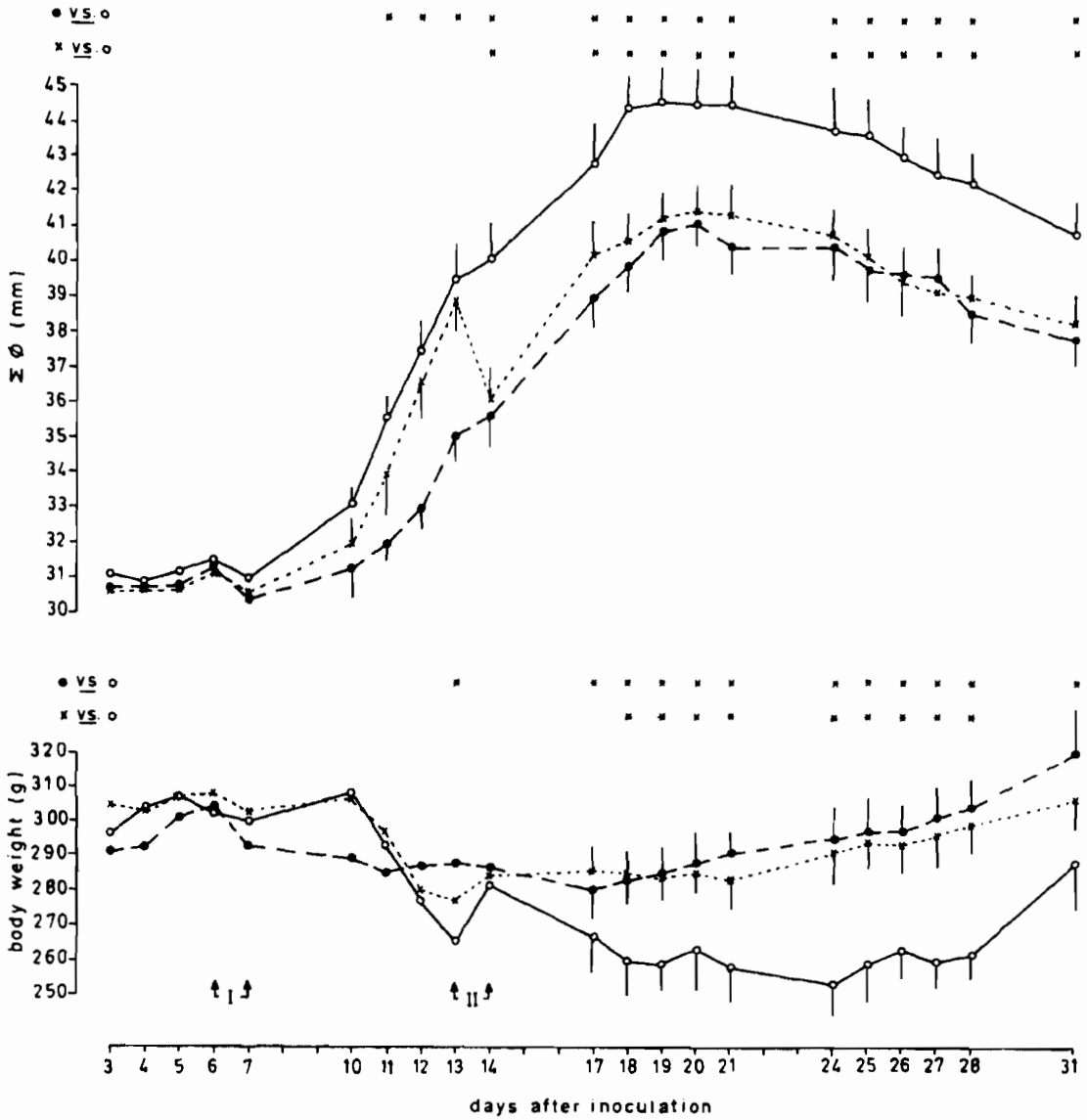

Fig. 6. Diameter of paws and joints (upper panel) and body weight (lower panel) in rats that were inoculated with *M. butyricum* on day 0 of the experiment. Experimental animals received 20, 40 and 80 mg/kg capsaicin (s.c.) on days 6 and 7 (EI group, dots, n = 18) or on days 13 and 14 (EII group, x, n = 22). The control groups received vehicle injections (circles, n = 25). Data are expressed as the mean. S.E.M. bares are indicated. An asterisk indicates 1-tailed $P < 0.05$ (Mann-Whitney U test). (Reproduced from Colpaert F.C., Donnerer, J. and Lembeck, F., Life Sciences, 32 (1983) 1827–1834, with permission from the authors and Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, UK.)

TABLE II

DEGREE OF JOINT INJURY IN THE HINDLIMB OF ARTHRITIC RATS WITH SELECTIVE LESIONS OF THE PERIPHERAL NERVE

(Reproduced from Levine et al., J. Neurosci., 6 (1986) 3423–3429, with permission from the authors and Oxford University Press, New York)

Treatment	Radiographic score [a] (%)					Mean	P [b]
	n	0	1	2	3		
None (controls)	60	5	15	33	47	2.4	
Capsaicin	42	26	12	29	33	1.8	< 0.05
Guanethidine	22	76	5	14	5	0.5	< 0.001
Reserpine	12	66	17	17	–	0.5	< 0.001

[a] Radiographic scoring based on the scale of Ackerman et al. (1979). 0 = no effect; 1 = mild effect; 2 = moderate effect; 3 = severe effect. Values indicate the percentage of rats in a treatment group with that score.

[b] Versus no treatment (control) group.

vere when the rats received capsaicin either on days 6 and 7 postinoculation (curve connecting dots) or on days 13 and 14 postinoculation (curve connecting x). Levine et al. (1986a) found less severe skeletal damage in polyarthritic rats pretreated with capsaicin on neonatal day 2 (impairment of afferent fibres) and also after impairment of the sympathetic innervation. Table II shows the radiographic examination of the rats indicating that severe damage was less frequent than in control rats after impairment of afferent fibre function (and efferent fibre function, see Section V). Inman et al. (1989) were also able to reduce the severity of bovine serum albumin-induced arthritis in the cat when the bovine serum albumin was co-injected with capsaicin into the articular space. Neurogenic components may also be important in the pathophysiology of the acute arthritis. The carrageenan-evoked extravasation of Evans Blue (as part of the inflammatory process) was reduced by 40% in rat knee joints which were injected with capsaicin 1–5 weeks before or denervated 10 days earlier (Lam and Ferrell 1989a). Whilst a contribution of SP in these processes has been suggested, CGRP may also contribute to the development and/or severity of some types of arthritis since immunization of rats against CGRP resulted in a less severe expression of lesions in chronic polyarthritic rats, at least in later stages (Louis et al. 1989).

Conflicting data do, however, exist since no reduction in the development of FCA-induced polyarthritis was observed following the application of capsaicin to neonatal rats in other studies (Hara et al. 1984; Cervero and Plenderleith 1987). Hara et al. (1984) found no difference in the foot swelling between capsaicin- and vehicle-treated animals, suggesting that the afferent denervation did not impair the local inflammatory reaction. Ambulatory and rearing activities, however, were much higher in capsaicin-pretreated arthritic animals and capsaicin pretreatment also reduced the body weight loss. Cervero and Plenderleith (1987) found that the onset, time course and severity of the arthritic reaction and the nociceptive thresholds were not different between normal rats and rats with neonatal capsaicin treatment. The different conclusions concerning the effect of afferent fibres on the severity of inflammation may be partly due to monitoring of different parameters, e.g., gross physical affects versus neurological affects.

The attention of research groups interested in neurogenic inflammation has concentrated on substance P. Levine et al. (1984) found a higher mean concentration of SP-li in the capsule of the rat ankle than of the knee and this difference was correlated with the greater severity of inflammatory lesions in the ankle of polyarthritic rats. Infusion of SP into the knee increased the severity of the arthritic symptoms as evaluated by radiographs (Levine et al. 1984). Pretreatment of rats by injection of a SP antagonist into the knee was shown to result in a 93% reduction of the inflammatory response to carrageenan whilst intra-articular injection of SP itself evoked an inflammatory response (Lam and Ferrell 1989a). The SP-evoked extravasation was suppressed by capsaicin, and a depletion of SP receptors in the joint was proposed as possible mechanism (Lam and Ferrell 1989b). The anti-inflammatory effect of gold salts which are used therapeutically in human joint disease may be related to its neurotoxic effect on peptidergic afferents since intramuscular injections of gold sodium thiomaleate in the rat produced a significant depletion in the SP-li content of the sciatic nerve (Levine et al. 1988) and a small nerve fibre neuropathy (Levine et al. 1986c). All these findings suggest that SP may play an important role in the inflammatory response of the joint and they support the idea that neurogenic mechanisms contribute to the expression of inflammatory reactions. Whilst much work has examined the role of SP in models of joint inflammation more work remains to be done to determine whether other neuropeptides present in primary afferents contribute significantly to the development and maintenance of inflammatory states.

II.E.4. Neuropeptides in human joint diseases

Some studies on human synovial tissue seem to support the experimental evidence that neuropeptides are released during joint disease. The picture emerging from clinical studies is, however, not totally clear and more data are necessary to provide definitive evidence linking different neuropeptides to human pathologies. Devillier et al. (1986), for example, found a higher mean level of tachykinin-li (e.g., SP) in inflammatory fluids (rheumatic diseases) than in non-inflammatory fluids. Marshall et al. (1990) showed that plasma levels

of ir-SP were significantly enhanced in patients with Reiter's syndrome, rheumatoid arthritis and osteoarthritis. In the same study the ir-SP concentration in synovial fluid exceeded the plasma concentration (except in Reiter's disease) indicating that synovial fluid was probably the source of the raised ir-SP level. The concentration of ir-SP was not assessed in synovial fluid from uninflamed joints. Conflicting results were obtained by Larsson et al. (1989) who were unable to measure SP-li either in the synovial fluid of 5 non-inflamed knees nor in the synovial fluid of patients with inflamed knees. NKA-li was detected in normal knees but not in inflamed ones and CGRP-li was detected in all inflamed and in 3 of 5 normal knees. All inflamed knees but only one normal joint had high levels of NPY-li (Larsson et al. 1989). It is difficult, however, to make firm statements from these data due to the small sample sizes. A further study reported significantly higher levels of VIP-li in the fluid of inflamed knee joints than in the serum of patients but no change in pancreatic polypeptide-li or SOM-li (Lygren et al. 1986). The authors suggested that VIP may be released from leucocytes and that this peptide may play a role in inflammation. The concentration of VIP-li was reduced after therapy with corticosteroids (Lygren et al. 1986). The significance of these findings is unclear and further studies are required to determine the role of each of these neuropeptides in the development and maintenance of human joint disease.

Attempts have been made in some studies to localize or measure neuropeptide content in the synovial tissue of patients with rheumatoid arthritis. In these tissue samples studied the authors found (1) a lower density of innervation in rheumatoid arthritis tissue than in tissue samples from non-inflamed joints and (2) a reduction in the content of neuropeptides such as ir-SP and ir-CGRP in tissues from rheumatoid arthritis patients (Grönblad et al. 1988; Mapp et al. 1990; Pereira da Silva and Carmo-Fonseca 1990). The depletion of neuropeptides was postulated to result from previous release of the peptides but it is unclear why in tissue samples of arthritic joints the innervation seemed to be less dense than in normal joints. Konttinen et al. (1990) and Hukkanen et al. (1991) argued that tissue of human material may not have been optimally treated for immunohistochemistry and studied, therefore, the density of innervation in the synovial tissue of ankle joints of normal and polyarthritic rats using proper fixation of the animals. In line with the observations in humans they found that the synovial tissue was less densely innervated in arthritic rats than in control animals (assessed by the marker PGP) and that tachykinin- and CGRP-positive elements were less concentrated in arthritic joints.

In summary different proportions of afferent (and efferent) fibres supplying joints show staining for neuropeptides, e.g., CGRP-li, SP-li and others. Studies on the release and functions of neuropeptides have concentrated on SP. This neuropeptide may be released upon activation of the fibres and produce vascular effects such as plasma extravasation. These effects seem to be mediated by NK_1 receptors and they may be involved in inflammatory reactions in the joint. A number of other effects such as activation of inflammatory cells may be produced as well. There is evidence that neuropeptides such as SP contribute to the severity of inflammatory lesions although further work is required to determine the precise stage at which the particular neuropeptides are involved and how interfering with their actions might alter the course of inflammatory lesions in joints in man.

III. Spinal mechanisms

Fig. 1 highlights the importance of the spinal cord as an integrative site for sensory and reflex functions. Evidence is accumulating that the spinal cord shows a great deal of plasticity during the development of inflammatory and other types of lesions which ultimately leads to the modification of spinal processing of afferent input and hence to changes in the output from the spinal cord. Thus the spinal cord actively contributes to nociceptive processing and is dependent on afferent, spinal and supraspinal components. This is important for the understanding of pain mechanisms involved in painful disorders and individual components may be exploited for therapeutic intervention. The next sections will describe the spinal neurones involved in articular nociception, and subsequent sections will address the inflammation-associated alterations in the cord.

III.A. Spinal projection and termination of articular afferents

III.A.1. Segmental distribution

The spinal projection of articular afferents of some big joints has been investigated with electrophysiological recordings and by using the retrograde transport of horseradish peroxidase (HRP) as a tracer. Using both of these techniques it was shown in the cat that the afferents of the knee in the MAN entered the spinal cord via the dorsal roots L5 and L6 whereas those in the PAN entered via L6, L7 and sometimes S1 (Gardner 1948; Skoglund 1956; Clark and Burgess 1975; Craig et al. 1988). A sparse projection of HRP-labelled fibres was found caudally as far as S2, and rostrally up to L1, with a dense projection of the PAN into the medial portion of Clarke's column (Craig et al. 1988). In the monkey labelling was identified in the dorsal roots L4-S1 after injection of HRP into the knee joint cavity

(Wiberg and Widenfalk 1991) whilst in the rat injections of HRP into the elbow joints labelled neurones in dorsal root ganglia C4-T4 with a maximum in C7-T1 (Widenfalk et al. 1988). In a similar study injections of HRP into the temporomandibular joint in rats labelled the dorsal root ganglia at the level C2-C5 (Widenfalk and Wiberg 1990). It seems therefore that each large joint projects to several spinal segments.

III.A.2. Intraspinal termination

Several studies have identified the sites of termination of joint nerves in the spinal cord. Electrophysiological recordings have revealed that most types of thick myelinated afferents of cat knee were found to terminate within the adjacent lumbosacral and lower thoracic spinal segments although a few rapidly adapting knee joint afferents ascended in the dorsal columns (Clark 1972). The projection fields of the MAN and PAN of cat knee were identified in the cap of lamina I, in laminae V-VI and in the dorsal part of lamina VII in the segments adjacent to the entry roots using HRP. No evidence was found for a projection into the laminae II, III and IV. In general the pattern of intraspinal termination of MAN and PAN afferents was similar to that found with HRP labelling of muscle and visceral afferents in the cat (see Craig et al. 1988). By contrast the brainstem terminations of HRP-labelled axons originating in the temporomandibular joint of cats exhibited a different pattern since termination sites were observed in laminae I, II and III of the medullary dorsal horn (Capra 1987). In the rat Levine et al. (1984) compared the patterns of spinal termination of nerves in the ankle and knee joint. After injection of the knee no or only minimal labelling was found in the spinal cord but after injection of the ankle intense labelling was obtained in lamina I and the substantia gelatinosa of the fourth lumbar segment. None of the studies performed to date have correlated the spinal termination site and electrophysiologically identified types of joint afferents.

III.B. Response properties of spinal neurones with articular input

Electrical stimulation of the PAN of cat knee has been shown to excite interneurones (Gardner et al. 1949; Lundberg et al. 1978; Harrison and Jankowska 1985; Schaible et al. 1986), motoneurones (Eccles and Lundberg 1959b; Holmquist and Lundberg 1961; Hongo et al. 1969; Fedina and Hultborn 1972; Johannson et al. 1986) and neurones of the spinocerebellar (Haddad 1953; Lindström and Takata 1972; Kuno et al. 1973; Belcari et al. 1974) and spinocervical tract (Harrison and Jankowska 1984) in the lumbar spinal cord. Most of these experiments have been performed in order to investigate spinal reflex pathways (see Section IV). In studies which have characterized the natural afferent input to ascending tracts, e.g., spinothalamic (Meyers and Snow 1982; Dougherty et al. 1992), spinomesencephalic (Yezierski and Schwartz 1986) and spinoreticular tract (Fields et al. 1977; Maunz et al. 1978) neurones have been identified which were driven by mechanical stimuli applied to the joint region as well as by mechanical stimuli applied to other structures, e.g., skin and muscle. Only very few systematic studies have, however, attempted to describe the particular laminar locations, response properties and convergence patterns of spinal neurones with joint input, and little effort has been made to correlate them with nociception.

III.B.1. Receptive fields of neurones with joint input

In the cat spinal cord neurones with knee input were mainly identified in the laminae I, IV-VI, VII and VIII (Rexed 1952) of the segments L4–S1 (Schaible et al. 1986, 1987a). The receptive fields of most neurones were found not to be restricted to the knee. When they were tested using natural stimuli they showed convergent inputs from either the knee and adjacent deep structures (muscles) in thigh and lower leg or from the knee joint, muscles and in addition the skin (Schaible et al. 1987a). Cutaneous receptive fields were mainly observed in neurones in the dorsal horn and were in most cases located near the knee itself although in some instances they were remote, e.g., on the foot. Comparisons of the sizes of receptive fields of neurones with joint input have shown that higher centres of the brain may regulate the receptive field size by suppressing synaptic activity. For example in cats with intact spinal cords deep dorsal and ventral horn neurones usually had receptive fields which were confined to the ipsilateral hindlimb (Schaible et al. 1991b) whereas in the spinalized cord a proportion of them had an additional receptive field in the contralateral hindlimb (Schaible et al. 1987a, 1991b; Neugebauer and Schaible 1990). Similar neurones with articular input have also been identified in rats with intact spinal cords (Grubb et al. 1993). A subset of convergent neurones in the subnucleus caudalis of the trigeminal nucleus with electrically, mechanically, and chemically identified inputs from the temporomandibular joint have been described. In addition to inputs from the joint these neurones also responded to mechanical stimulation of the facial skin and some intraoral structures (Broton et al. 1988).

III.B.2. Activation thresholds of neurones with joint input

By analogy to the classification of neurones with cutaneous input (Dubner and Bennett 1983; Willis 1985; Besson and Chaouch 1987) the neurones with input from cat's knee have been classified as nociceptive-specific (NS) and wide-dynamic-range (WDR) neu-

rones according to their thresholds and their responses to innocuous and noxious stimuli applied to the joint, other deep tissue and skin. Under this classification NS neurones with articular input are those which respond only to noxious compression of the joint and other structures of the hindlimb(s) and to noxious movements of the knee (movements against the resistance of the joint structures). Alternatively they respond mainly to noxious stimuli and generate only few impulses following application of innocuous stimuli (Schaible et al. 1987a, 1991b; Neugebauer and Schaible 1990). WDR neurones show substantial responses to innocuous pressure applied to the knee and other structures and to movements in the working range of the knee but show more pronounced responses to stimuli of noxious intensity (Schaible et al. 1987a, 1991b; Neugebauer and Schaible 1990). Many NS neurones with knee input have been located in the laminae VII and VIII and some of them are ascending tract cells (Schaible et al. 1987a,b; Neugebauer and Schaible 1990). This is in line with earlier studies describing ascending nociceptive cells with predominant or exclusive deep input located in the deep dorsal and ventral horn (Fields et al. 1977; Meyers and Snow 1982). WDR neurones were most often found in the deep dorsal horn, e.g., laminae V and VI (Schaible et al. 1987a; Neugebauer and Schaible 1990).

Broton et al. (1988) classified neurones with input from the temporomandibular joint in the rat according to the mechanical thresholds in the cutaneous receptive fields as either NS or WDR. LTM (low threshold mechanoreceptive) cells responding only to innocuous stimuli received less input from the joint than WDR or NS neurones. The inflow from the temporomandibular joint to trigeminal NS and WDR neurones was regarded as nociceptive since (1) responses to electrical stimulation of the joint nerve had a high threshold and a long latency which is indicative of small fibre activation, (2) responses to local mechanical stimuli at the joint, if tested, required high intensity and, (3) activity could be evoked by algesic compounds which activate small diameter afferents (Broton et al. 1988).

In summary, the nociceptive afferent input from joints is processed in the spinal cord in different types of neurones. With regard to the 'sensory channels' activated by joint input there are two subsets of neurones, one that has only inputs from deep structures including the joint (see also Yu and Mense 1990a,b) and another one which has additional cutaneous input. Many neurones which have only input from deep structures (muscles, joints) seem to be nociceptive specific. It may be speculated, therefore, that this type of neurone is important for discriminative aspects of pain in the deep tissue since its activation is clearly related to the presence of a damaging stimulus in joint and/or muscle. It is clear, however, that this point of view is

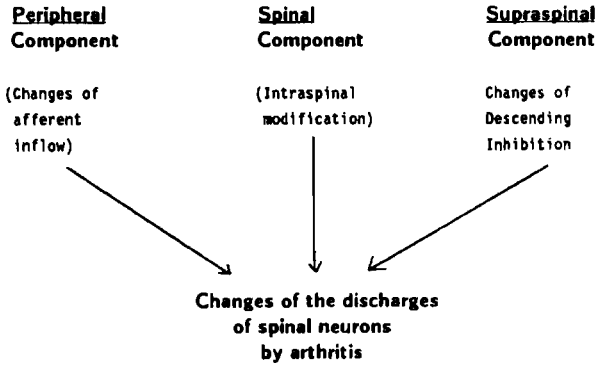

Fig. 7. Schematic display of the components that contribute to the changes of discharges in spinal neurones during arthritis.

rather simplistic since there is no reason to exclude the large number of neurones with convergent inputs from deep tissue and skin from an important role in nociception in the joint. Indeed, the activity in descending pathways may have an influence whether a neurone is characterized as an NS or WDR neurone (see Section III.D.2) and both types of neurones show considerable changes in their response properties during the development of inflammation (see below). At the moment, therefore, both types of neurones should be studied since both of them may be important for the mediation of pain in the joint. The data provide, however, some explanation for the diffuse and badly localized nature of joint pain (see Section I.A.).

III.C. Reponse properties of spinal neurones during joint inflammation

Since an inflammation of the joint induces quantitative and qualitative increases in the afferent input to the spinal cord one might expect that the discharge properties of spinal neurones would also be altered as a consequence. The response properties of the spinal neurones during inflammation, however, do not just reflect the afferent impulses from the joint on a spike for spike basis. Fig. 7 shows that at least three major components may interact and determine the actual changes of the response properties in the course of inflammation. The contribution of 'central mechanisms' to spinal cord discharges postinjury in the peripheral tissue has been postulated by Hardy et al. (1952a,b) and Woolf (1983) has provided direct experimental evidence for the importance of 'central mechanisms'. Brief stimulation of afferent C fibres caused changes of excitability in motor reflexes and expansions of receptive fields in dorsal horn neurones which outlasted the actual stimulus (Woolf 1983; Cook et al. 1987). The presence of 'central changes' implies that there are not only alterations in the afferent drive of central neurones but that the sensitivity to the afferent inputs in the central neurones themselves is enhanced.

Changes in the discharge properties of spinal neurones during inflammation were first documented in rats with FCA-induced chronic polyarthritis (Menetrey and Besson 1982). Subsequent studies have been performed in cats and monkeys where changes in the discharge properties of spinal cord neurones have been directly monitored during the development of an acute inflammation in the joint induced by the injections of kaolin and carrageenan into the knee (Schaible et al. 1987b; Neugebauer and Schaible 1988, 1990; Dougherty et al. 1992). A further study has addressed changes in the response properties of neurones in rats with unilateral chronic inflammation at the ankle (Grubb et al. 1993). The next paragraphs will first describe the results obtained in the model of acute inflammation in the joint and then the data collected in the chronic models.

III.C.1. Acute inflammation in the joint

In the spinalized cat inflammation-induced changes in the discharge properties and receptive field characteristics of spinal cord neurones have been directly documented in long-term recordings (Schaible et al. 1987b; Neugebauer and Schaible 1988, 1990). Ascending and non-ascending neurones with knee input were identified in the deep dorsal and ventral horn and characterized before and during the development of the inflammation induced by the intra-articular injections of kaolin and carrageenan into the knee. Typically the neurones showed changes in their responses to stimulation of the injected knee, such that responses to innocuous and noxious stimuli were enhanced in WDR neurones and the threshold in NS neurones was lowered to a point where they could be activated by light and normally innocuous stimuli. Fig. 8 shows typical examples of these changes in an ascending NS neurone (in A) and in an ascending WDR neurone (in B) with knee joint input, both of which were located in the laminae VII/VIII. After injection of kaolin and carrageenan into the joint the NS neurone developed a response to flexion of the injected knee and the WDR neurone showed an increase to flexion of the inflamed joint (top graphs in A and B). The majority of the neurones in the deep dorsal and ventral horn (20 of 23) also showed changes in their responses to stimuli which were applied to regions adjacent to the knee (thigh and lower leg) and remote from the knee (paw and contralateral leg). The neurone in Fig. 8B, for example, also exhibited increased responses to flexion of the contralateral normal knee. Some neurones showed an expansion of the total receptive field during development of inflammation in the joint. When the inflammation developed in the injected knee the magnitude of the responses to electrical stimulation of the sural nerves and descending axons in the spinal cord showed an increase (Fig. 8, bottom graphs). The enhanced

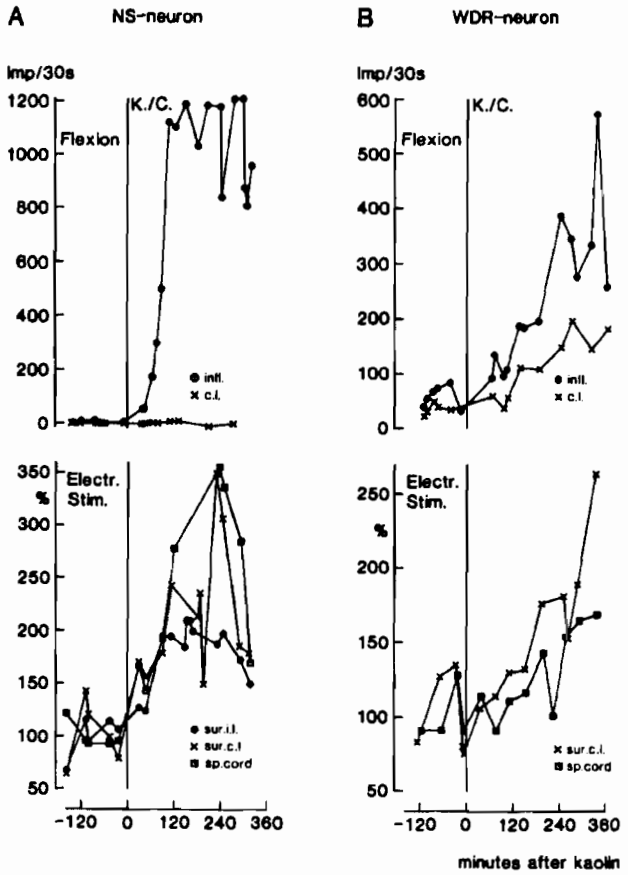

Fig. 8. Induction of hyperexcitability in a spinal nociceptive specific neurone (in A) and in a wide dynamic range neurone (in B) with knee input during developing inflammation of the knee joint. Both neurones were recorded from for several hours. The top graphs show the responses of these neurones to flexion of the ipsilateral (i.l.) and the contralateral (c.l.) knee. At the time point 0 min the inflammatory compounds kaolin and carrageenan (K./C.) were injected into the ipsilateral knee. The bottom graphs show the responses of these neurones to electrical stimulation of the sural nerve(s) and descending axons in the spinal cord. For electrical stimulation the responses in the control period were averaged and the mean was set 100%. All values in the control and inflammatory period were then expressed as percentage of the control mean. The spinal cord was stimulated with impulses of 5 (A) and 3V (B) (duration 0.2 msec). Stimulation of the sural nerves was sufficient to evoke 'A-responses' in the spinal neurones (latencies between 10 and 25 msec). Selected voltages were kept constant throughout the experiments. (Reproduced from Neugebauer, V. and Schaible, H.-G., J. Neurophysiol., 64 (1990) 299–311, with permission from The American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, USA.)

responses to these constant test stimuli clearly show the development of hyperexcitability in these neurones. Inflammation-induced changes have also been documented in spinothalamic tract neurones in laminae I-V in the monkey (Dougherty et al. 1992). With a similar time course as in the cat there was an increase in the resting discharges, in the responses to flexion of the injected knee (8 of 12 cells), in the responses to pinching of cutaneous receptive fields (8 of 11 neurones) and

a modest increase in the responses to brushing the skin (6 of 12 neurones). Collectively the spectrum of changes suggests that spinal neurones with joint input are rendered hyperexcitable to their afferent inputs (see below).

III.C.2. Chronic inflammation

In chronic models of inflammation changes in the discharges of spinal cord neurones are more difficult to identify since the alterations in the discharge properties have to be extracted from the comparison of samples of the population of neurones. In decerebrate, spinal rats with FCA-induced polyarthritis (between 15 and 43 days postinoculation) neurones were identified in the superficial dorsal horn (laminae I and II) which were either driven from non-oedematous skin or from oedematous areas (Menetrey and Besson 1982). The discharge properties of neurones with input from normal skin were similar to those of neurones in normal rats since their receptive fields were small and restricted to the distal extremity of the limb and they responded maximally to noxious stimuli. Approximately one-third (6 of 17) of these neurones were nociceptive specific and most had no ongoing discharges in the absence of stimulation. By contrast neurones with input from inflamed skin had larger receptive fields, including the surrounding region of the ankle. All of these neurones responded to light mechanical stimuli (touch, pressure and/or transarticular pressure) and some gave maximal responses to light stimuli. In addition, most of these neurones had a high level of background activity, frequently showing bursting pattern. In the deep dorsal horn (laminae III-VI) the neurones appeared either 'normal' or they had large receptive fields and high background discharges. In anaesthetized non-spinalized rats with the same type of joint inflammation two subpopulations of neurones in the deep dorsal horn, one with 'typical' response properties and another with 'atypical' response properties have also been identified in the deep dorsal horn, at 3–4 weeks postinoculation, indicating that many inflammation-induced changes in the response properties of spinal neurones were not abolished by descending inhibitory pathways (Calvino et al. 1987a,b; see also Section III.D.).

Alterations in the discharge properties of spinal cord neurones have recently also been studied in anaesthetized rats with a unilateral chronic inflammation in the ankle region induced by FCA (Grubb et al. 1993). A significant reduction in the mechanical threshold of neurones with input from the ankle and the surrounding structures was found in neurones of the superficial and deep dorsal horns and of the ventral horn at all stages of inflammation. Receptive field size also increased in these experiments since there was a progressive increase in the proportion of neurones with ankle input which had receptive fields in the thigh, the tail, abdomen and in the contralateral leg. A higher proportion of neurones were activated by brushing when the ankle was inflamed. The general increase in neuronal excitability observed was also accompanied by the development of resting discharges in a higher proportion of neurones at days 2 and 20, although it should be noted that discharge frequencies were similar to those seen in control animals (Grubb et al. 1993).

The basic findings are summarized in Table III. All these data suggest the importance of intraspinal mechanisms that enhance the sensitivity of the spinal neurones. By these mechanisms the processing of nociceptive input from the inflamed joint shows a large amplification in the spinal cord. The concept of 'central sensitization' was also supported by studies on lamina I cells in a chronic model of inflammation (Hylden et al. 1989) and by studies on the responses of spinothalamic neurones to capsaicin-induced skin lesions (Simone et al. 1991). The exact nature of the 'central mechanisms' has still to be defined and there is a wide range of possibilities, e.g., presynaptic mechanisms (spatial and temporal summation by the additional afferent input, release of 'inflammatory' mediators) and postsynaptic mechanisms (synaptic and intracellular events that enhance excitability) which might explain many of the observations that have been made. The importance of the afferent input for the expression of the 'central component' is supported by the observation that neurones without knee input did not change their respon-

TABLE III

CHANGES IN THE RESPONSE AND RECEPTIVE FIELD PROPERTIES OF SPINAL NEURONES DURING ARTHRITIS

(1) Increased responsiveness to stimuli applied to the inflamed joint
  - Lowering of threshold in NS neurones with development of responses to gentle innocuous stimuli, enhanced responses to noxious movements
  - Enhanced responses in WDR neurones to innocuous and noxious stimuli
(2) Increased responsiveness to mechanical stimuli applied to areas adjacent to the joint
(3) Increased responsiveness to mechanical stimuli applied to areas remote from the injected joint (including enlargement of the total receptive field)
(4) Increased responses to electrical stimulation of peripheral nerves and descending axons in the spinal cord
(5) Induction or increase of ongoing discharges

siveness to mechanical (and electrical) stimuli during development of inflammation in the knee (Neugebauer and Schaible 1990). Future studies will have to determine whether the spinal components may, by themselves, become targets for therapeutical interventions and thereby achieve pain relief.

III.D. Inhibitory influences on spinal neurones during arthritis

The activity in many spinal cord neurones is inhibited by a variety of inputs. Inhibitory effects are often mediated by inhibitory interneurones which are relay neurones for afferent and/or descending pathways. Inhibition of nociceptive spinal neurones is thought to be relevant in analgesic mechanisms since experimental activation of inhibitory systems may reduce or abolish the nociceptive processing in the spinal cord. Still pain states occur in humans in spite of the presence of inhibitory systems. The role of inhibitory systems in painful disorders should be addressed. Are they dysfunctional in clinical pain states or is the capacity of inhibitory systems diminished? An important question is whether inhibitory influences are activated in the presence of inflammation. The next sections will describe changes of inhibitory influences on spinal neurones in models of inflammation in animals.

III.D.1. Heterotopic inhibitory influences

In the dorsal horn of normal rats convergent neurones (WDR neurones) but not non-nociceptive and proprioceptive neurones, were inhibited by noxious stimuli applied to heterotopic body areas, i.e., those applied to distant body regions remote from the excitatory receptive fields (LeBars et al. 1979a,b). From these and other observations the concept of diffuse noxious inhibitory controls (DNIC) has emerged (see LeBars and Villanueva 1988 for details). A similar inhibition of 'typical' convergent neurones by heterotopic stimuli has also been observed in the polyarthritic rat but in these animals 'atypical' convergent and 'atypical' non-noxious neurones were also suppressed by heterotopic stimuli. Importantly, gentle stimulation of the contralateral inflamed ankle, a stimulus intensity which is ineffective in normal animals, was shown to be capable of triggering inhibition of both typical and atypical neurones (Calvino et al. 1987b). It was concluded that the input for triggering heterotopic influences by mechanical stimuli is altered in arthritic rats and it was assumed that this was due to a lowering of mechanical threshold of articular afferents in inflamed joints (Calvino et al. 1987b). In an associated behavioural study the responses to viscero-peritoneal nociceptive stimuli were reduced in rats which had developed polyarthritic lesions compared to normal animals. The degree of reduction in the writhing behaviour observed was correlated with the degree of mechanical hyperaesthesia suggesting a possible heterotopic inhibitory influence arising in arthritic lesions (Calvino and LeBars 1986).

III.D.2. Descending inhibition

It is now well established that at least under experimental conditions many spinal cord neurones are under tonic descending inhibitory control which effectively reduces spinal nociceptive processing (for reviews see Fields and Basbaum 1978; Gebhart 1986; Willis 1985, 1988; Besson and Chaouch 1987). Tonic descending inhibition has also been described for spinal cord neurones with afferent input from the knee, in both normal cats and in cats with an acute inflammation in the knee (Cervero et al. 1991). In these animals tonic descending inhibition may also determine the size of the receptive fields of the spinal neurones and/or the excitation thresholds since neurones with input from the knee in spinalized cats tended to have larger receptive fields than those in intact cats (Neugebauer and Schaible 1990; Schaible et al. 1991b). A clear example of this was found in a group of neurones (10 of 15) which showed a weak response to innocuous stimuli during cold-block reversible spinalization but responded only to noxious stimuli when the cold-block was removed. In the same experiments the excitatory receptive fields expanded to the ipsilateral paw when the spinal cord was cold-blocked in one-half (9 of 17) of the neurones (Schaible et al. 1991b).

During the development of an acute inflammation in the knee the effectiveness of tonic descending inhibition was found to be increased. In 14 experiments 14 neurones in the intact spinal cord were monitored during the development of an acute inflammation and cold blocks were used to assess the amount of descending inhibition in one and the same neurone prior to and during development of inflammation (Schaible et al. 1991b). These experiments demonstrated that most NS and WDR neurones in laminae IV-VIII are under an increasing amount of descending inhibition during the first hours of a developing inflammation. In general the expression of hyperexcitability was less pronounced in the intact than in the spinalized state although the basic phenomenon of hyperexcitability was similar (see previous paragraph). These results suggest that the hyperexcitability evoked by inflammation is counteracted by an increase in the effectiveness of tonic descending inhibition (Fig. 7). It is not yet known whether this increase in the effectiveness is due to an increased inflow from supraspinal structures or whether the spinal neurones develop an increased sensitivity for the inhibitory input, in parallel to an increase of sensitivity for the excitatory drive from the periphery. It is also not clear how the balance between the excitatory and inhibitory components is adjusted during chronic