arthritis. An analysis of transmitters involved in descending inhibition (e.g., 5-HT, noradrenaline) has shown that they are present in increased concentrations in the spinal cords of polyarthritic rats suggesting that descending inhibition may be increased in the long-term range in these animals (see Section III.E.3 and 4).

In summary there is evidence for an increase in heterotopic influences on spinal neurones with input from inflamed areas. Furthermore recordings which have been made in anaesthetized cats show the ability of descending inhibitory influences to reduce the increase of hyperexcitability during arthritis. The mode of activation and the dynamics of the descending inhibition in the natural biological context is still open. It may be speculated, however, that the expression of pain is to some extent modified by the activation of these descending influences, by reflex mechanisms and/or by conscious processes and by heterotopic inhibitory influences.

III.E. Cellular mechanisms in joint inflammation: ions, neurotransmitters, neuromodulators and gene expression

The analysis and understanding of the intraspinal processes involved in inflammation-induced hyperexcitability is far from complete due to the complex nature of this matter. The processes involved may include (1) changes in the ionic environment of neurones, (2) the effects of fast-acting transmitters and slowly acting modulators on distinct receptor types, (3) the activation of intracellular second and third messenger systems, (4) additional mechanisms such as gene expression (see also Dubner and Ruda 1992). This section summarizes mechanisms and changes which have been identified in the spinal cord of experimental animals with acute or chronic inflammatory lesions in joints.

III.E.1. Extracellular ion concentration

III.E.1.a. Extracellular $[K^+]_o$. Electrical stimulation of myelinated and unmyelinated afferent fibres (Ten Bruggencate et al. 1974; Czeh et al. 1981) and the application of noxious stimuli to the skin (Sykova et al. 1980) lead to transient elevations of the potassium concentration in the spinal cord (measured with ion-sensitive microelectrodes). Changes of the potassium concentration show a close relationship to the appearance of field potentials (Somjen 1979; Sykova 1983). $[K^+]_o$ was also elevated during innocuous flexion of the knee joint and during electrical stimulation of myelinated group II and III fibres in the PAN, and a small additional component has been found when noxious stimuli were applied to the joint or when unmyelinated fibres in the PAN were electrically stimulated (Heinemann et al. 1990). During the development of an acute inflammation in the knee induced by kaolin and carrageenan the stimulus-evoked elevation of $[K^+]_o$ was found to increase by about 25% (Heinemann et al. 1990). In general the absolute $[K^+]_o$ level reached depended more on the site and type of stimulation than on the actual stimulus intensity itself (Heinemann et al. 1990). The authors concluded that changes in $[K^+]_o$ were unlikely to explain the changes of excitability in the course of inflammation although a contribution of this mechanism may exist. By contrast long-term increases of $[K^+]_o$ were observed by Svoboda et al. (1988) in 75% of the spinal cords of rats following subcutaneous injection of formalin or turpentine into the hindpaws and these authors proposed that rises in extracellular $[K^+]_o$ may play a substantial role in the changes of excitability during injury.

III.E.2. Excitatory amino acids

In the central nervous system glutamate acts at postsynaptic NMDA (*N*-methyl-D-aspartate) or non-NMDA receptors (Mayer and Westbrook 1987; Evans 1989; Aanonsen et al. 1990; Headley and Grillner 1990). Following electrical stimulation of peripheral nerves the responses of spinal cord neurones to single A- and C-fibre volleys were effectively blocked by non-selective antagonists of excitatory amino acids showing that excitatory amino acids are involved in the spinal processing of afferent input (Schouenborg and Sjölund 1986; Schneider and Perl 1988). The application of specific NMDA antagonists did not block the responses to electrical stimulation of afferent nerve fibres in neurones in the superficial dorsal horn indicating that non-NMDA receptors are sufficient for the (monosynaptic) mediation of responses to afferent discharges in A and C fibres (Schneider and Perl 1988). A contribution of NMDA receptors has, however, been implicated in the 'wind-up' phenomenon which may occur in spinal cord neurones after repetitive stimulation of C fibres (Davies and Lodge 1987; Dickenson and Sullivan 1990; Thompson et al. 1990). Wind-up is a term used to describe successive increases in the magnitude of the responses of a neurone to a constant repeated stimulus, and this phenomenon was blocked by specific NMDA antagonists. This finding indicates that NMDA receptors may be involved in particular aspects of the nociceptive processing in the spinal cord. The contribution of NMDA receptors in spinal cord activity has also been examined by using natural noxious stimuli. Responses to noxious mechanical stimuli were shown to be suppressed in neurones in the ventral horn but not in the dorsal horn (Headley et al. 1987). In other studies NMDA receptors have been shown not to be involved in the processing of noxious mechanical information in the dorsal horn under 'normal circumstances' but seemed to contribute to delayed discharges after the injection of formalin into the

paw (Haley et al. 1990) and to discharges after occlusion of the femoral artery (Sher et al. 1990). Collectively these observations suggest that under particular conditions NMDA receptors may become more important in the nociceptive processing in the spinal cord. Biophysical studies indicated that the activation of NMDA receptors needs specific requirements (removal of Mg^{2+} which blocks the inactivated NMDA channel) (Mayer et al. 1987; Monaghan et al. 1989) and these could be achieved by injury-associated activation of nerve cells.

III.E.2.a. Excitatory amino acids and receptors in inflammation of the joint. A possible involvement of NMDA (and non-NMDA) receptors in the spinal processing of afferent activity from the inflamed joint has been studied in the cat and monkey which had developed a kaolin/carrageenan-induced inflammation in the knee joint. In the monkey glutamate-like activity was found to be increased in the lumbar spinal cord on the ipsilateral side to the injection 4, 6 and 8 h after induction (Sluka et al. 1992). Using a microdialysis probe in the lumbar dorsal horn of 10 monkeys the release of amino acids has also been measured using HPLC (Sorkin et al. 1992). After intra-articular injection of kaolin and carrageenan, the release of glutamate- and aspartate-like activity (and also glycine-and serine-like activity) was transiently increased above the basal level and this was followed by a second phase during which more prolonged changes in amino acid levels were observed which showed peaks 0.5–1.5 h after the injection of the knee. The secondary increases in amino acid levels were sometimes of greater magnitude than those immediately following the injection (Sorkin et al. 1992). Whilst these results show an increased turnover of glutamate and aspartate in the central nervous system some evidence was also obtained which indicated that the turnover of glutamate in joint afferents was increased. In these experiments the proportion of glutamate-containing fibres (mainly group III fibres) in MAN was shown to increase during the development of acute inflammation (Westlund et al. 1992) although it is not clear how this relates to the turnover of glutamate at the nerve terminal.

In order to test the excitability of spinothalamic tract cells with joint input for excitatory amino acids Dougherty et al. (1992) applied ionophoretically NMDA, quisqualate, glutamate and aspartate to 8 neurones and demonstrated excitatory effects. The responses to these excitatory amino acids showed changes within several hours of kaolin/carrageenan-induced inflammation. Whereas responses to quisqualate, glutamate and aspartate increased in 4 of 6 neurones (in parallel to increased responses to mechanical stimulation) the responses to NMDA were reduced in 6 of 7 neurones. By contrast, following the intradermal application of capsaicin (which also increased responsiveness of spinothalamic cells) the responses to NMDA were enhanced (Dougherty and Willis 1992). The reasons for these differences remain to be clarified.

Schaible et al. (1991a) examined whether the discharges in spinal neurones with input from the inflamed joint could be reduced by NMDA antagonists. The NMDA antagonists ketamine (applied i.v. and ionophoretically) and D-2-amino-5-phosphonovalerate (AP-5, applied ionophoretically) were found to reduce activity in about 70% of 71 neurones in the deep dorsal and ventral horn with input from the inflamed knee, in doses which suppressed the responses to ionophoretically applied NMDA but did not or only minimally reduce those to quisqualate. These effects occurred within a few minutes of drug application and consisted of either a reduction in the ongoing discharges and/or a reduction in the responses to mechanical stimulation of the knee such as flexion. Ketamine when applied i.v. was found to be the most effective drug probably due to the fact that ketamine and AP-5 could only act on 1 cell when applied ionophoretically. These results showed a significant contribution of NMDA receptors to spinal cord neurone activity in inflammation but do not exclude a contribution of NMDA receptors to the activity in these neurones under normal conditions. It was documented, however, in 9 neurones that i.v. ketamine partly reversed the inflammation-induced activity which was directly monitored during the development of the inflammation-induced hyperexcitability in some ascending neurones (Schaible et al. 1991a). These results suggest that hyperexcitability of spinal neurones during joint inflammation is at least in part a process which is dependent on continuous synaptic activation of NMDA receptors. The effects of the NMDA antagonists on the hyperexcitable neurones during inflammation could result either from a direct contribution of NMDA receptors to the depolarization of the neurones or from a reduction of the calcium influx (MacDermott et al. 1986; Mayer et al. 1987) which may reduce excitability of the neurones by intracellular events.

III.E.3. Serotonin, tryptophan and 5-hydroxyindoleacetic acid

Studies of these compounds are of interest since nociceptive processes in the spinal cord and pain are modulated via serotoninergic descending inhibitory systems (see Ruda et al. 1986). 5-HT is a metabolite of tryptophan (the primary substrate for the synthesis) and further metabolism of 5-HT results in the formation of 5-hydroxyindoleacetic acid (Cooper et al. 1986).

HPLC studies of extracts from homogenized spinal cord, brainstem and forebrain have shown that the basal levels of these three compounds were significantly higher in polyarthritic than in normal rats (Weil-Fugazza et al. 1979, 1980). The concentration of

5-HT was found to be increased in the dorsal and ventral horns of the spinal cord of arthritic rats, and in general this appeared to be related to an increase in serum tryptophan availability (Weil-Fugazza et al. 1980; Godefroy et al. 1987). One conclusion of these studies was that in chronic arthritic states and in chronic pain the descending serotoninergic system to the dorsal horn is more activated (Godefroy et al. 1987). In a subsequent study the analysis was confined to the superficial layers of the spinal cords of normal and polyarthritic rats (3 weeks postinoculation). In the superficial dorsal horn of arthritic rats only 5-hydroxyindoleacetic acid was elevated whereas the levels of tryptophan and 5-HT were not different in normal and arthritic animals (Godefroy et al. 1990). An enhancement of 5-HT-li in the lumbar spinal cord of polyarthritic rats has also been observed in immunocytochemical studies (Schoenen et al. 1985; Marlier et al. 1991). In some of the polyarthritic rats studied 15, 30 and 60 days postinoculation Schoenen et al. (1985) found heavier 5-HT-li in laminae I, VIII and in the ventro-medial group of motoneurones. Marlier et al. (1991) performed an image analysis of sections treated immunocytochemically for detection of 5-HT and elevated levels of 5-HT-li were detected in laminae I/II and III/IV from 2 weeks to 4 months postinoculation. Indeed there was almost a doubling in the levels of 5-HT-li in laminae I and II at 1 month in the arthritic animals compared to controls. Although these studies differ to some extent (e.g., laminar localization of elevated levels) they agree in that the serotoninergic system seem to be more active in polyarthritic rats.

Weil-Fugazza et al. (1979) tried to influence the levels of tryptophan and 5-hydroxyindoleacetic acid by i.v. administration of morphine in normal and arthritic rats. Tryptophan and 5-hydroxyindoleacetic acid levels were increased 1 hour after the subcutaneous application of 10 mg/kg morphine, and this increase was more pronounced in arthritic animals. The authors concluded that there is an activation of the 5-HT metabolism in animals suffering from chronic pain and that there is a greater modification of the 5-HT metabolism in arthritic animals by morphine. Lower doses of morphine did not, however, change the levels of tryptophan and 5-hydroxyindoleacetic acid, neither in the superficial nor in the deep dorsal horn, and this suggests that the analgesic effect of low doses of morphine does not involve the activation of serotoninergic descending inhibition (Godefroy et al. 1990).

III.E.4. Norepinephrine and uric acid

Some nerve fibres which descend from the brainstem to the spinal cord are known to use norepinephrine (noradrenaline) as one of their neurotransmitters (see Ruda et al. 1986) and in order to study possible modifications of this system the level of norepinephrine in the spinal cord has been compared in normal and polyarthritic rats (6 weeks postinoculation) by HPLC analysis of homogenized spinal cords (Weil-Fugazza et al. 1986). Six weeks postinoculation the levels of norepinephrine and uric acid were significantly higher in spinal cords of arthritic rats than in cords of normal rats, and in addition the rate of disappearance of noradrenaline in the dorsal part of the cord in arthritic rats was increased. These results suggest an activation of descending adrenergic systems during chronic polyarthritis and they indicate that changes occur in purine catabolism (Weil-Fugazza et al. 1986). An interaction of noradrenergic pathways with the analgesic action of opioids during conditions of acute cutaneous inflammation has recently been shown in behavioural experiments in which intrathecal application of the alpha$_2$-adrenoceptor antagonist idazoxan blocked the antinociceptive effect of morphine (Hylden et al. 1991). Evidence supporting these observations comes from experiments where adrenal medullary implants in the spinal cord of polyarthritic rats reduced vocalizations when the system was stimulated with nicotine; this effect was assumed to be opioidergic since naloxone completely blocked the nicotine-stimulated reduction in vocalizations (Sagen et al. 1990).

III.E.5. Neuropeptides

In the spinal cord a considerable number of neuropeptides has been identified which are contained in central terminals of afferent fibres and/or intrinsic interneurones and/or axons of descending neurones (Luttinger 1984; Ruda et al. 1986; Besson and Chaouch 1987; Duggan and Weihe 1991). Some of them have been shown to be intraspinally released, either spontaneously or by electrical stimulation of afferent nerve fibres and/or different noxious stimuli (Duggan and Weihe 1991). Neuropeptides may have either presynaptic effects influencing the release of other transmitters such as glutamate (Kangra et al. 1990) and/or postsynaptic actions causing excitation (e.g., SP) or inhibition (e.g., SOM, some opioid peptides) of spinal cord neurones. Compared to the rapid action of excitatory amino acids the onset of the postsynaptic effect of peptides is usually slow and the duration of the effect may outlast the period of application (Duggan and Weihe 1991). Neuropeptides may also stimulate molecular events such as gene expression in neurones (Williams et al. 1989).

Of particular interest are the recent observations that the neuropeptide content of some dorsal root ganglia and spinal cord neurones may change during arthritis or other inflammatory lesions. The precise functional implications of these alterations have not been adequately determined but it is worth noting that changes in the content of neuropeptides are not always

tightly linked to the development of inflammatory lesions. Until it is determined whether discrepancies are due to technical problems (e.g., sensitivity of assays) or to dynamic changes in the different phases of inflammation firm conclusions seem to be premature. The following section will summarize studies on neuropeptides with special reference to their involvement in inflammation.

III.E.5.a. Tachykinins. Within the group of the mammalian tachykinins, i.e., SP, NKA, NKB (Maggio 1988), most attention has been directed to SP since it was the first one postulated to be involved in nociception. SP-li is contained in afferent fibres including joint afferents (see Section II.E.), intrinsic spinal neurones and descending axons (see Luttinger 1984; Ruda et al. 1986; Duggan and Weihe 1991).

III.E.5.a.i. Upregulation in inflammation. In the polyarthritic rat peripheral nerves, dorsal root ganglia (Lembeck et al. 1981; Colpaert et al. 1983) and spinal cord (Colpaert et al. 1983; Schoenen et al. 1985; Marlier et al. 1991) contained higher levels of SP-li. Schoenen et al. (1985) described more intense SP-li staining in laminae I, II and X of the spinal cord 15, 30 and 60 days postinoculation with a maximal effect at the 30 day time-point. Image analysis of immunohistochemically treated sections of the spinal cord (Marlier et al. 1991) showed an increase to 11–17% over control in SP-li levels in laminae I and II of lumbar segments between 1 and 4 months postinoculation. These changes were not, however, seen 2 weeks postinoculation even though inflammatory symptoms were already present at this stage indicating that changes in peptide content do not always follow the development of the experimental disease. By contrast Chery-Croze et al. (1985) found SP-li unchanged in the dorsal half of the cord and reduced in the ventral cord of polyarthritic rats 20 days postinoculation. SP-li levels were elevated (+69%, radioimmunoassay) in the dorsal root ganglia C6–7 of rats with unilateral FCA-induced inflammation in the region of the carpal joint 15 days postinoculation (no changes in the contralateral dorsal root ganglia; Smith et al. 1992).

Thus most studies agree that the synthesis of SP-li is elevated during arthritis or similar inflammation but it is not clear whether the inflammatory symptoms and the changes in SP-li are tightly linked. Clear evidence for a rapid increase in the biosynthesis of SP-li after injection of adjuvant into the paw was provided by measuring the levels of the mRNA encoding preprotachykinin A (PPT-A) (Minami et al. 1989). The levels of PPT-A mRNA were significantly increased in the dorsal root ganglia at L4-L6 levels and the lumbar spinal cord, and these changes were present as early as day 1 postinoculation. The upregulation of the synthesis may in fact be initiated immediately after a damaging stimulus. Indeed, within 3 h after the injection of

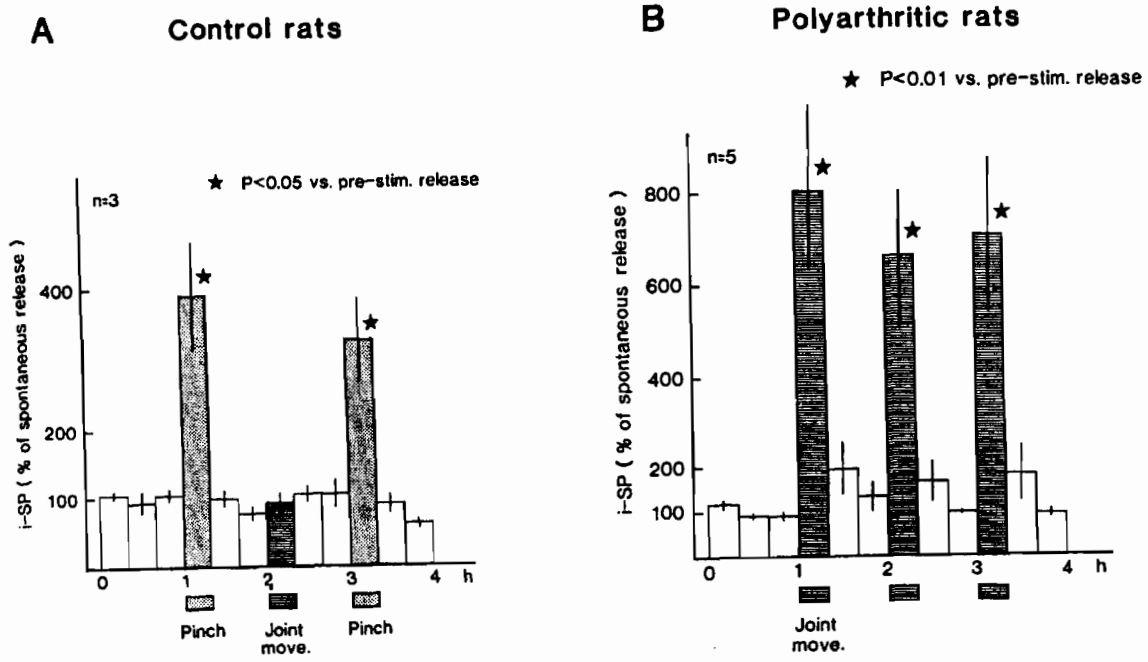

Fig. 9. Release of ir-SP from the lumbar dorsal horn in normal rats (A) and polyarthritic rats (B). Ir-SP was analysed in the perfusate collected in the dorsal horn with a push-pull cannula. The tip of the cannula was located at a depth of 0.7 mm from the dorsal surface. The stimuli were noxious pinch of the skin and forced movements of the ankle joint. Samples were collected at 20-min intervals. Noxious pinching of the skin was performed at a frequency of 1/min (for 30 sec) for 20 min and the ankle joint was flexed and extended for 15 sec each with pauses of 15 sec, for 20 min. (Reproduced and modified from Oku, R., Satoh, M. and Tagaki, H., Neurosci. Lett., 74 (1987) 315–319, with permission from the authors and Elsevier Science Publishers BV, Amsterdam, The Netherlands).

formalin into the rat paw the number of dorsal root ganglia which reacted positively for preprotachykinins, the precursors of SP and other tachykinins was increased (Noguchi et al. 1988). The SP binding sites in the spinal cord seem to be reduced in polyarthritic rats (Mantyh et al. 1988).

III.E.5.a.ii. Release of tachykinins. The intraspinal release of ir-SP in vivo has been studied in the decerebrate polyarthritic rat, 2–3 weeks after inoculation, using an in situ spinal cord perfusion method (push-pull cannula) (Oku et al. 1987) and in the cat, within the first hours of a developing kaolin/carrageenan-induced inflammation in the knee, using antibody-coated microprobes (Schaible et al. 1990). In the cat the release of ir-NKA which is encoded together with SP-li by the PPT-A gene and is coexistent with SP-li in a subset of neurones (Maggio 1988; Duggan and Weihe 1991) has also been investigated (Hope et al. 1990a). Both studies demonstrated increased intraspinal release of ir-SP under inflammatory conditions. Oku et al. (1987) found an increased basal release of ir-SP in polyarthritic rats and significant release over baseline during forced movements of the ankle joint (considered as innocuous in normal animals). By contrast forced movements did not evoke release of ir-SP in the normal rat whereas noxious pinching of the skin did. The difference in the release of ir-SP in normal and polyarthritic rats is displayed in Fig. 9. In the cat neither ir-NKA nor ir-SP were released into the spinal cord when the normal joint was stimulated by innocuous mechanical stimuli such as light pressure and movements within the working range but after induction of arthritis these stimuli caused release of both peptides. Although ir-NKA and ir-SP appeared first in the superficial dorsal horn, in the area where numerous joint afferents terminate (Craig et al. 1988), ir-NKA seemed to spread within the whole grey matter whereas ir-SP stayed more close to the initial zone of detection, i.e., the superficial dorsal horn and up to the dorsal surface of the cord. Another difference between these peptides was that the release of ir-SP seemed to be stimulus-related whereas ir-NKA was also present in the absence of mechanical stimulation. Persistence and spread of ir-NKA in cat spinal cord was also observed when the peptide release was evoked by electrical stimulation of tibial nerve and by brief noxious mechanical stimuli of the toes (Duggan et al. 1990; Hope et al. 1990b). Recent data suggest that intraspinal peptidases may account for these differences in the persistence and spread of ir-SP and ir-NKA (Duggan et al. 1992; Schaible et al. 1992). Sluka et al. (1992) have studied SP-li in the spinal cord of the monkey at different time points after injection of kaolin and carrageenan into the knee. The side to side difference was greater in the lumbar dorsal horn than in the cervical dorsal horn with a reduction of SP-li in the lumbar dorsal horn ipsilateral to inflammation at 4 and 6 h after joint injection. This decrease in SP-li was thought to result from release of the peptide.

The release studies indicate that ir-SP is predominantly released from high-threshold afferents which are sensitized and then respond to innocuous mechanical stimuli such as flexion. Since ir-SP was mainly released in a stimulus-dependent mode it may have a role in the stimulus-related processing of nociceptive information from the inflamed joint. It is unlikely, however, that ir-SP is critical in the early stages of the inflammation-evoked hyperexcitability since it was usually not detected until neuronal hyperexcitability in the kaolin/carrageenan model was established (see Section III.C.1). The distribution of ir-NKA within the spinal cord shows that peripheral stimulation may lead to release of compounds which persist in the cord a considerable time beyond the period of stimulation. The function of ir-NKA is not known but presumably it may rather have a tonic modulatory than a stimulus-related effect.

III.E.5.b. Calcitonin gene-related peptide. CGRP-li in the dorsal horn is mainly if not exclusively located in central terminals of afferent fibres (Ruda et al. 1986; Duggan and Weihe 1991). In rats with FCA-induced polyarthritis the amount of CGRP-li has been determined in the dorsal root ganglia, the dorsal and ventral horns by radioimmunoassay of the extracted peptide 15, 26 and 40 days postinoculation (Kuraishi et al. 1989). In the dorsal root ganglia CGRP-li was almost doubled 15 and 26 days postinoculation but had returned to normal by day 40. By contrast inflammatory signs (decrease in nociceptive mechanical threshold and increase in the hind-paw volume) were present at days 15 and 26–40. These authors were unable, however, to detect any changes in CGRP-li levels in the dorsal and ventral horn of the same animals (Kuraishi et al. 1989). Somewhat different results were found in another study on polyarthritic rats in which image analysis was performed on lumbar spinal cord sections treated with antibodies directed against CGRP (Marlier et al. 1991). In these experiments CGRP-li was increased by 10–25% over control values in laminae I and II between 1 and 2 months postinoculation. It should be noted, however, that 2 weeks after inoculation CGRP levels were still normal even though clinical symptoms of arthritis were already evident. In rats with unilateral FCA-induced inflammation in the carpal joint CGRP-li levels were also elevated in the ipsilateral dorsal root ganglia C6–7 (+204%, radioimmunoassay) but not in the contralateral controls 15 days postinoculation (Smith et al. 1992). Whilst these studies have shown an increase of CGRP-li at chronic stages of inflammation an increase of the proportion of dorsal root ganglion cells with CGRP-li has not only been observed at a chronic stage of a unilateral inflam-

mation at the ankle (20 days) but also at the second day after inoculation of FCA (Hanesch et al. 1993). In another study capsaicin-evoked release of ir-CGRP in dorsal half slices of the lumbar cord was found to be enhanced in polyarthritic rats (days 15–20 postinoculation) compared to control rats (Nanayama et al. 1989).

In the monkey CGRP-li has been studied in the spinal cord at several time points during the development of an acute kaolin/carrageenan-induced inflammation in the knee. Using a computer assisted quantification system a significant decrease of 31.5% in CGRP-li in the lumbar versus the cervical dorsal horn was found at 8 h after induction of inflammation but at no earlier time points suggesting release of ir-CGRP at a later stage of an acute inflammation (Sluka et al. 1992).

III.E.5.c. Opioid peptides and opioid receptors. Opioid peptides are derived from three large, genetically distinct precursor peptides, pro-opiomelanocortin, pro-enkephalin and pro-dynorphin (Borsodi 1991). In the spinal cord enkephalins (derived from pro-enkephalin) and dynorphins (derived from pro-dynorphin) have been identified (Borsodi 1991). These peptides are contained in some intrinsic spinal cord neurones but other neuronal elements which stain positive with the appropriate antibodies may be afferent and descending fibres (Ruda et al. 1986; Duggan and Weihe 1991). The three main types of opioid receptor, mu-, delta- and kappa-receptors (Borsodi 1991; Przewlocki 1991) are present in the spinal cord (Vaught 1991).

III.E.5.c.i. Behavioural studies. A number of behavioural studies in the rat employing nociceptive tests have suggested that a polyarthritis leads to changes in the antinociceptive effects of opioids and, in some respects, a different pattern of behavioural effects. Firstly, in polyarthritic rats the antinociceptive effect of morphine has been shown to be enhanced compared to control rats (Kayser and Guilbaud 1981, 1983; Neil et al. 1986; Millan et al. 1987). This effect is displayed in Fig. 10 which shows the morphine effects upon the threshold for vocalization in normal and arthritic rats. Very low doses of morphine were found to evoke a paradoxical hyperalgesic effect in similar experiments (Kayser et al. 1987). These changes in the antinociceptive effect of morphine in the polyarthritic rat were mainly observed in the paw pressure-vocalization test, a suprasegmentally integrated test, and not in the paw withdrawal test, a spinally coordinated reflex (Kayser and Guilbaud 1990). Supersensitivity to the antinociceptive effect of morphine was also observed in the paw pressure withdrawal test in rats with unilateral chronic inflammation of the paw (Millan et al. 1988). Secondly, on repeated administration of morphine polyarthritic rats develop tolerance to a greater extent than do normal animals (Kayser and Guilbaud 1985;

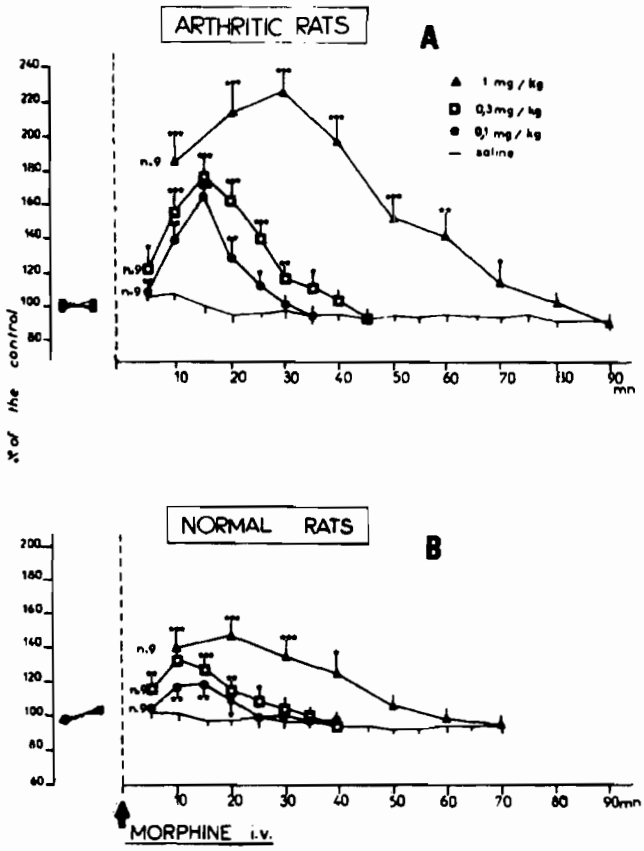

Fig. 10. Mean curves of morphine effects upon the threshold for vocalization in normal and polyarthritic rats. All injections were given intravenously into the tail. The stimulus was pressure applied to the left hindpaw. The values obtained for each test are expressed as percentages of the control values before morphine injection (±S.E.M.). Discontinued lines illustrate mean curves obtained with saline. Student's *t* test method used for the statistical analysis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. (Reproduced from Kayser, V. and Guilbaud, G., Brain Res., 267 (1983) 131–138, with permission from the authors and Elsevier Science Publishers BV, Amsterdam, The Netherlands.)

Kayser et al. 1986a,b) and thirdly, naloxone in extremely low doses is also antinociceptive in polyarthritic rats (Kayser and Guilbaud 1981).

In some studies specific agonists have been used in order to identify the receptors responsible for the antinociceptive effects of opioid peptides in normal and polyarthritic rats. In the polyarthritic rat Neil et al. (1986) found a reduction in vocalization after pressure was applied to the inflamed paw with the mu-agonist (D-Ala^2, *N*-Me-Phe^4, Gly^5-ol)-enkephalin (DAMGO) and the kappa-agonist U50,488H but not with the delta-agonist DTLET. In these experiments tolerance developed to both DAMGO and U50,88H during the course of the experiment. Conflicting data were obtained by Millan et al. (1988) who found that the antinociceptive effect of U50,488H was attenuated in paw and tail pressure test in the same arthritic model. When applied intrathecally DAMGO also produced an

increase in the level of antinociception in acute carrageenan-evoked cutaneous inflammation whereas U50,488H was only antinociceptive with systemic application (Hylden et al. 1991). In summary, there is general agreement as to the action of mu-agonists in arthritic animals but there is conflicting data for agonists acting at delta- and kappa-receptors.

In order to reveal changes in the actions of endogenous opioids specific antagonists have been administered in arthritic animals in an attempt to unmask their physiological effects. In behavioural experiments the responses to application of mechanical and heat stimuli to the paw or the tail in the normal rat were unchanged by the non-selective opioid-antagonists naloxone, the delta-antagonist ICI-154,159 and the kappa-antagonist MR2266, indicating that there was no change in nociceptive thresholds. In the polyarthritic rat, however, the kappa-antagonist MR2266 significantly decreased the response thresholds for pressure applied to the paw and the tail whereas neither naloxone nor ICI-154,159 had an effect (Millan et al. 1985, 1987, 1988). None of the antagonists had an effect on the heat threshold (Millan et al. 1987, 1988). MR2266 and naloxone reduced the mechanical threshold when mechanical stimuli were applied to the paw in rats with unilateral chronic paw inflammation although the effect of naloxone was only seen in the first 24 h and was not observed when the long-term polyarthritic lesions developed (Millan et al. 1988). In subsequent experiments Millan and Colpaert (1991) implanted osmotic minipumps containing naloxone into rats which had a unilateral chronic inflammation and found that naloxone only potentiated hyperalgesia at doses which suppressed the effect of kappa-agonists in addition to mu-agonists (Millan and Colpaert 1991).

The studies with antagonists suggest that the activity of agonists at the kappa-receptor undergoes marked changes whereas endogenous agonists at other receptors are not similarly influenced and the possible use of kappa-agonists in the therapy of chronic pain has been alluded to (Shippenberg et al. 1988; Millan and Colpaert 1991). On the other hand the marked antinociception of exogenous mu-agonists in polyarthritic rats should be noted. Presumably these results cannot be simply explained with activation or inactivation of receptors. Rather the metabolism of opioid peptides has to be taken into account. In the polyarthritic rat an enhancement of the antinociceptive potency of systemically administered kelatorphan which is an inhibitor of the enkephalin metabolism has also been found indicating an upregulation of the enkephalinase enzyme in this situation (Kayser et al. 1989).

III.E.5.c.ii. Upregulation of opioid peptides in the spinal cord. The systemic application of opioids in behavioural experiments does not allow conclusions to be made about the site of action. Evidence is accumulating, however, that some of these changes may be related to alterations within the spinal cord. In an electrophysiological study on spinalized polyarthritic rats naloxone was found to induce a highly significant increase in the spontaneous firing and the responses to electrical stimulation of C fibres in dorsal horn neurones suggesting tonic activity of a spinal cord intrinsic opioid system in this chronic pain model (Lombard and Besson 1989). Several groups have reported pronounced alterations in the synthesis of spinal endogenous opioid peptides during chronic arthritis and other types of chronic inflammation. In the poly- and monoarthritic rat the synthesis of ir-pro-dynorphin in the lumbosacral spinal cord is markedly increased (Millan et al. 1985, 1987, 1988; Höllt et al. 1987; Weihe et al. 1989) and rats showing the greatest mechanical hyperalgesia in the paw pressure test displayed the greatest rise in the level of ir-dynorphin (Millan et al. 1985). This activation was illustrated as an intensification of the immunohistochemical staining for dynorphin and alpha/beta-neo-endorphin. Whereas perikarya were rarely stained in control animals and were encountered only in laminae I and II many strongly stained perikarya were found in laminae I and II and also in laminae IV and V in arthritic rats (Weihe et al. 1988, 1989). Stained fibres were also seen throughout the dorsal and ventral grey matter in normal rats but during arthritis this staining was much more pronounced. These changes were well localized since biochemical and immunhistochemical changes were bilateral in the polyarthritic rat but unilateral in the monoarthritic animal (Weihe et al. 1989). A similar activation of pro-dynorphin synthesis has also been found in unilateral acute and chronic inflammation of the hindpaw, with pronounced changes occurring within the first days (Iadarola et al. 1988a,b,c; Millan et al. 1988; Ruda et al. 1988; Przewlocka et al. 1992). In the superficial dorsal horn of rats with unilateral paw inflammation a higher proportion of ascending neurones in lamina I and of non-ascending neurones in laminae I and II were found to be immunoreactive for dynorphin A1–8 (Nahin et al. 1989).

Whilst marked changes in the synthesis and immunocytochemical staining for dynorphin have been seen, there seems to be a comparatively small but significant increase in the concentration of opioid peptides derived from pro-enkephalin A in rats with chronic arthritis. Cesselin et al. (1980, 1984) found an increase of about 60–80% in the concentration of ir-Met-enkephalin in the dorsal and ventral halves of the cervical and lumbar enlargement of the spinal cord. Similar results were obtained by Millan et al. (1985) but this change was not correlated with the intensity of mechanical hyperalgesia. In the monoarthritic rat the level of ir-Met-enkephalin was elevated (about 50%) in the segments receiving the afferent input from the

inflamed limbs (Faccini et al. 1984). An increase of the (pre)pro-enkephalin mRNA was shown in earlier stages (first days) of a unilateral FCA- (Iadarola et al. 1988a,b,c; Przewlocka et al. 1992) and carrageenan-induced inflammation in the rat hindpaw (Noguchi et al. 1992). By contrast Millan et al. (1988) reported a small rise of ir-Leu-enkephalin and ir-Met-enkephalin only at a later stage (5 weeks) of a chronic unilateral FCA-induced inflammation.

Quite how these changes in peptide expression are related to function is not clear but it should be noted that the absolute production and the amount of peptide released are not the only important factors. As mentioned above, persistence and breakdown are important as is the concentration of receptors at the target site (see below). In addition, the increase in the level of these opioid peptides is not necessarily associated with an increase in the turnover of the peptide. Studies on the release of ir-Met-enkephalin from slices of the lumbar enlargement have shown that increases in the levels of ir-Met-enkephalin in spinal cord of polyarthritic rats are associated with a lower fractional rate constant of the ir-Met-enkephalin release suggesting that the spinal ir-Met-enkephalin turnover is reduced in chronically suffering animals (Cesselin et al. 1984). When the intrathecal space was perfused in normal and polyarthritic rats (4th week) a marked reduction (−56%) in the spontaneous outflow of ir-Met-enkephalin was noted in arthritic rats but movements of the legs and raising extracellular potassium in the intrathecal space still produced a significant increased release. It was concluded that in arthritic rats the basal activity but not the stimulus-evoked release of enkephalinergic neurones is reduced (Bourgoin et al. 1988). By contrast, basal release of ir-Met-enkephalin-Arg^6-Gly^7-Leu^8 from spinal cord isolated from rats with unilateral FCA-induced hindpaw inflammation was enhanced in the first days after inoculation whereas the K^+-stimulated release was not altered (Przewlocka et al. 1992). The basal and the K^+-stimulated release of ir-alpha-neoendorphin (derived from pro-dynorphin) were enhanced (Przewlocka et al. 1992).

III.E.5.c.iii. Binding sites in the spinal cord. Cesselin et al. (1980) found the total number of binding sites for naloxone and Leu-enkephalin and receptor affinity to be unchanged in polyarthritic rats. In another study, however, there was a rise in the number of mu-receptors and a significant fall in the number of kappa-receptors in the spinal cord whereas delta-receptors remained unaltered (Millan et al. 1986). By contrast, rats with unilateral inflammation of the paw showed no change in the density of mu-, delta- and kappa-binding sites in the lumbar cord ipsilateral to the inflammation nor was the laminar pattern changed (Iadarola et al. 1988c; Millan et al. 1988). The concentration of neutral endopeptidase EC 3.4.24.11., and the number of mu- and delta-binding sites in the spinal cords were found not to be altered in arthritic animals compared to normal rats (Delay-Goyet et al. 1989). From this result and the observation that the release of Met-enkephalin-like material is reduced in the arthritic rat (Cesselin et al. 1984) it has been suggested that the greater analgesic response of mu-agonists in arthritic animals is most likely due to a decreased occupation of binding sites by endogenous enkephalins; in this situation exogenously administered selective mu-agonists should produce a better analgesic response (Delay-Goyet et al. 1989).

III.E.5.d. Somatostatin. SOM-li is contained in afferent fibres and in intrinsic spinal neurones (Ruda et al. 1986; Duggan and Weihe 1991). Changes in the levels (measured by radioimmunoassay) of ir-SOM-14 and ir-SOM-28 have been investigated in the dorsal root ganglia and the spinal cord of the polyarthritic rat. The content of ir-SOM, especially ir-SOM-14, was found to be enhanced in the dorsal root ganglia at L4–L6 levels in the 4th week after inoculation but not at earlier or later time points (Ohno et al. 1990). This increase was prevented by chronic administration of the NSAID sodium diclofenac (Ohno et al. 1990) which reduces the severity of adjuvant-induced polyarthritis. By contrast no change in the levels of ir-SOM was found in the dorsal root ganglia of rats with unilateral FCA-induced inflammation in the carpal joint 15 days postinoculation (Smith et al. 1992) and the reasons for these differences have not been identified. Despite these increases in the levels of ir-SOM in the dorsal root ganglia of polyarthritic rats Ohno et al. (1990) were unable to detect any changes in the levels of ir-SOM in the spinal cord of these animals.

III.E.5.e. Other peptides. In their study on the polyarthritic rat (day 22) Chery-Croze et al. (1985) found increased cholecystokinin levels in the dorsal half of the cord (compared to control rats) but no change in the ventral half. By contrast the staining for VIP was found not to be altered in the polyarthritic rat compared to controls. Similarly, no differences were reported for the levels of ir-vasopressin and ir-oxytocin in the lumbosacral spinal cord of polyarthritic rats compared to control rats (Millan et al. 1984). Schoenen et al. (1985) have, however, reported an enhancement of FRAP activity in lamina II in the polyarthritic rat.

III.E.6. C-fos proteins

Recently the expression of 'proto-oncogenes' such as c-*fos* and their protein products have been identified in nerve cells of the spinal cord of animals following noxious stimulation of peripheral tissues and electrical stimulation of peripheral nerves (Hunt et al. 1987; Bullitt 1990). Although the function of these proteins is not precisely known it is postulated that they are involved in long-term adaptations in neurones (Hunt et

al. 1987; Morgan and Curran 1989; Williams et al. 1989).

With regard to nociception in the joint the expression of c-*fos* has been studied in the spinal cord of rats. After injection of mustard oil into the knee joint Williams et al. (1989) found strong c-*fos* staining in spinal segments L2-L6 which was most intense in lamina I and only weak in lamina V. The expression of c-*fos* has also been studied 16 h after implanting urate crystals close to the ankle joint (this treatment resulted in an acute inflammatory episode in the ankle and adjacent areas). C-*fos* labelled cells were found from L1 through L6, ipsilateral to the inflamed paw, in lamina I, the lateral neck of the dorsal horn, at the base of the dorsal horn, and in laminae VII, VIII and X (Menetrey et al. 1989). A similar pattern of labelling was found after injection of Freund's adjuvant into the plantar surface of the hindpaw (Menetrey et al. 1989). In polyarthritic rats c-*fos*-li in the lumbar enlargement was found to be correlated with the development of adjuvant-induced arthritis and hyperalgesia (Abbadie and Besson 1992). Fig. 11 shows that c-*fos*-li was absent at 1 week postinoculation (preclinical stage), moderate to strong at 2–3 weeks (acute stage of inflammation with significant hyperalgesia), decreased at 11 weeks (recovery stage) and back at control levels at 22 weeks (normalization). Under these conditions most intense labelling was found in the laminae V and VI of the deep dorsal and in the ventral horn whereas only few labelled neurones were identified in the superficial dorsal horn.

From these data it is clear that there is a widespread rostrocaudal distribution of neurones in the dorsal and ventral horn that express c-*fos* during a localized or more generalized inflammation. The pattern of the labelling (superficial dorsal horn vs. deep dorsal and

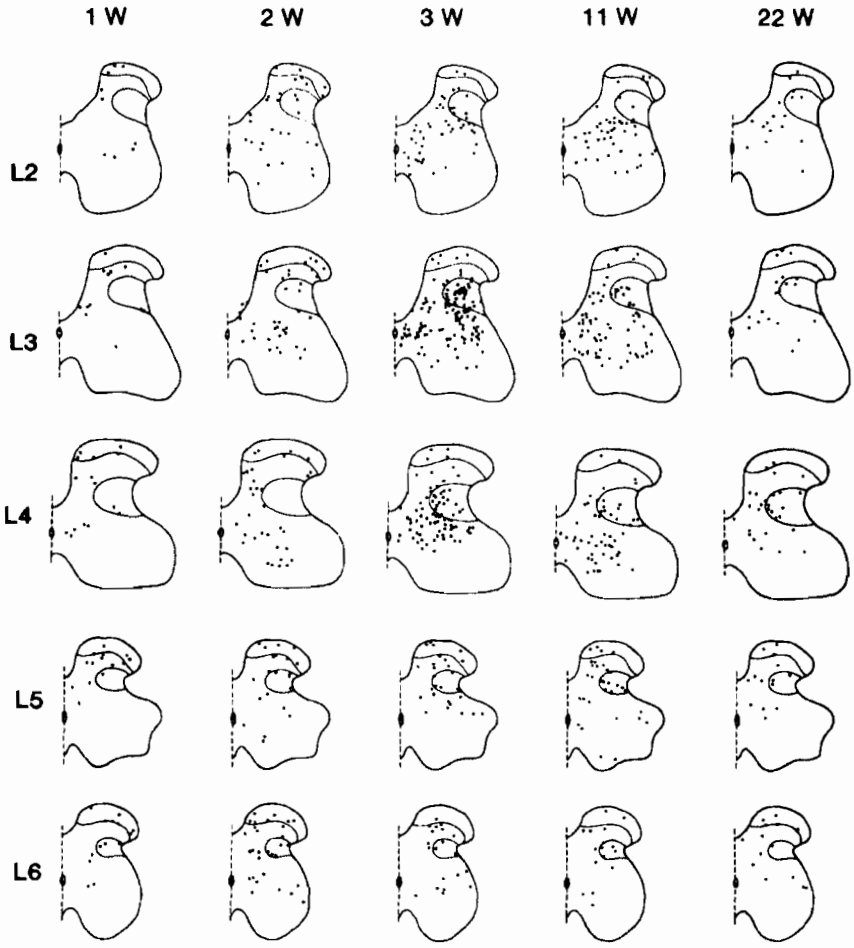

Fig. 11. Camera lucida drawings showing the rostrocaudal distribution of *Fos*-li neurones in the lumbar spinal enlargement at different times postinjection of Freund's adjuvant into the base of the tail. Five segments, from L2 to L6, and 5 postinjection times: 1 week (1W) 2, 3, 11 and 22 weeks, are represented. Each scheme includes all labelled cells in 3 × 40 μm sections; each dot represents 1 labelled cell. These data show c-*fos* that is expressed 'spontaneously', i.e., without any intentional stimulation. Control sections showed no *Fos*-li and are not represented. The boundaries of the superficial laminae and of the reticular part of the neck of the dorsal horn are outlined for orientation. (Reproduced from Abbadie, C. and Besson, J.-M., Neuroscience, 48 (1992) 985–993, with permission from the authors and Pergamon Press Ltd, Headington Hill Hall, Oxford OX3 0BW, UK.)

ventral horns) is obviously dependent on the duration of inflammation. Although the expression of c-*fos* (and other proto-oncogenes) seems to be evoked by damaging stimuli the precise relationship to nociception-associated events is still open (which types of neurones show expression of c-*fos*?, which are the adequate stimuli ?) and the functional consequences are still under investigation. Among other things the expression of c-*fos* may be coupled to dynorphin and enkephalin gene transcription (see Dubner and Ruda 1992).

In summary, a number of transmitters, neuromodulators and receptors seem to be involved in the spinal cord activity relevant in the processing of nociceptive input from the joint. Furthermore the presence of an acute or chronic inflammation in the joint may significantly influence levels of transmitters and neuromodulators in the dorsal root ganglia and the spinal cord. Although many particular aspects are known the current knowledge is not sufficient to give a full description of the events in the spinal cord which are associated with inflammation in the joint. There is evidence that the excitatory transmitter glutamate plays a role in the transmission of information from the joint in the spinal cord and this processing seems to involve NMDA receptors, at least under inflammatory conditions. Biochemical data suggest an increase of the biosynthesis of transmitters which are involved in descending inhibition of the spinal neurones (5-HT, norepinephrine). The synthesis of some neuropeptides such as ir-SP, ir-CGRP, ir-dynorphin and ir-enkephalin in the dorsal root ganglia and/or the spinal cord is also increased, at least in some stages of inflammation, and intraspinal release of some neuropeptides in the course of inflammation has been demonstrated. Still the functional consequences have not been fully elucidated. Finally the inflammmation leads to the expression of 'proto-oncogenes' in spinal neurones which may regulate, among other things, the transcription processes in the synthesis of neuropeptides.

IV. Motor reflexes

Pain in the joint always influences motor performance in that extensive movements are avoided and the position is kept such that pain is minimized. Although this motor behaviour is probably generated at various supraspinal sites spinal motor reflexes may play a role as well. The motor reflex effects evoked by joint afferents have been comprehensively reviewed by Johansson et al. (1991) and the reader is referred for details to their recent review article. Motor reflexes may be considered as a feedback system from the joint back to the joint since sensory information arising in joints may influence the motor outflow to those muscles that move and stabilize the joint (Fig. 1). In this section data will be summarized which are related to joint inflammation.

IV.A. Reflexes evoked by stimulation of joint afferents

Reflexes in muscles of the limbs (measured by electromyography) and reflex discharges in motor neurones can be elicited by electrical stimulation of articular nerves (Gardner 1950; Eccles and Lundberg 1959a,b; Holmquist and Lundberg 1961; Hongo et al. 1969; Klineberg 1971; Fedina and Hultborn 1972; Ramcharan and Wyke 1972; Lundberg et al. 1978; Harrison and Jankowska 1985; Johansson et al. 1986) or by activation of receptors in the joint capsule and the joint ligaments or by pressure applied to, or inflation of the joint (Andersson and Stener 1959; Ekholm et al. 1960; Grigg et al. 1978; Shimamura et al. 1984; Baxendale et al. 1987, 1988). In other experiments the effect of different joint angle on reflexes evoked by stimulation of non-articular nerves has been studied (Cohen and Cohen 1956; Skoglund 1956; Freeman and Wyke 1976b; Grigg et al. 1978; Baxendale and Ferrell 1981, 1982). Reflexes evoked by joint afferents are important in eliciting protective muscle movements, i.e., movements counteracting hyperflexion, hyperextension, hyperrotation. These potentially noxious movements have marked effects on alpha-motoneurones whereas under normal conditions joint afferents only exert weak effects on the alpha-motoneurones. The application of innocuous stimuli to the joint, however, leads to considerable reflex discharges in gamma-motoneurones. Through this pathway joint afferents may participate in the regulation of joint stiffness and joint stability during normal movement (see Johansson et al. 1991). It may be speculated that the articular group II and the low-threshold group III units have an important role in the generation of these reflexes since they are activated by innocuous movements and many of them exhibit an immediate increase in their discharges when the joint is being moved to the extreme of the working range (see Dorn et al. 1991; Krauspe et al. 1992, and Section II).

IV.B. Effects of chemical stimulation and inflammation on motor reflexes

Several studies have shown that changes in the input to the motoneurones caused by chemical stimulants which activate fine afferent fibres or by the induction of joint inflammation changed the pattern of reflex responses in the spinal cord. For example, injections of the C-fibre stimulant, mustard oil into the joint was shown to produce a pronounced and prolonged increase in the excitability of alpha-motoneurones in decerebrate spinalized rats as determined by record-

ings made from the motor nerves supplying the biceps femoris and semitendinosus muscles. Although the motoneurones did not exhibit direct reflex discharges following mustard oil they showed increased responses to ipsi- and contralateral mechanical stimuli applied to the hindlimb (Woolf and Wall 1986). Similar effects were obtained when a kaolin/carrageenan-evoked arthritis developed in the knee joint of the cat. In the decerebrated low spinal cat electromyographic recordings of the flexion reflex elicited by electrical stimulation of the common peroneal nerve revealed an increase in the reflex intensity with a time course that matched the development of the inflammatory process as assessed by monitoring the intra-articular temperature. In addition changes in the pattern of reflex responses were observed during development of inflammation. The most obvious of these was that flexion evoked greater activity in knee flexor units than extension when the joint was inflamed whereas extension was a more powerful stimulus in normal joints. These changes were suggested to be of afferent origin since local anaesthesia of the joint reversed the inflammation-induced changes (Ferrell et al. 1988).

A more complex result was obtained when the reflex discharges were monitored in single identified alpha- and gamma-motoneurones of the biceps semitendinosus, during development of a kaolin/carrageenan-induced inflammation of the knee joint in the spinalized cat. In these experiments most of the gamma-motoneurones were excited when the normal knee joint was flexed. During the development of joint inflammation, however, about two-thirds of these neurones showed increased reflex discharges evoked by the same stimulus whilst the other third of the neurones to the same muscle developed inhibitory reflexes (He et al. 1988). The time course of both excitatory and inhibitory effects was similar following the time course of the sensitization of joint afferents and the development of hyperexcitability of spinal neurones with afferent input from the knee. The alpha-motoneurones showed similar but less pronounced changes (He et al. 1988).

In summary these results indicate that there is an increase in the flexion reflex during long-lasting noxious stimulation of the knee which is consistent with the nociceptive flexion reflex concept. A flexion reflex would, however, keep the joint in a position that would significantly activate sensitized joint afferents and thus produce a vicious circle of afferent activation and reflex motoneurone discharge. Injured or inflamed joints are, however, normally kept in mid position and movements are prevented if possible. In this respect the generation of the inhibitory reflex response (He et al. 1988) may be relevant since it would counteract the excitatory reflex discharge in other motoneurones and thus modify the stereotype flexion response in such a way that the joint can now be kept at a midrange position. In midrange position the nociceptive joint afferents are less activated when joints are inflamed.

V. Sympathetic reflexes

V.A. The sympathetic innervation of joints

Earlier we discussed the efferent functions of afferent nerve fibres supplying joints, and efferent motor pathways also influence nociceptive information coming from joints by regulating joint position. As with all structures the joint also receives efferent innervation from sympathetic fibres. Studies using axonally transported HRP have shown that big joints are supplied by efferent fibres arising from several sympathetic ganglia. In the rat the temporomandibular joint receives sympathetic fibres from the ipsilateral superior cervical and stellate ganglia (Widenfalk and Wiberg 1990), the elbow joint from the stellate ganglion and the T2-T4 ganglia of the ipsilateral sympathetic trunk (Widenfalk et al. 1988). The knee joint of the cat is supplied by sympathetic fibres from the paravertebral ganglia L4–L6 of the ipsilateral trunk (Heppelmann and Schaible 1990) and the knee joint in the monkey receives fibres from the sympathetic ganglia L3–S3 (Wiberg and Widenfalk 1991). Functionally the sympathetic fibres control the vascular tone in articular vessels since blood flow was found to be increased after elimination of the sympathetic innervation and was decreased during electrical stimulation of joint nerves (Cobbold and Lewis 1956; Sato and Schaible 1987; Ferrell et al. 1990). Concomitant with reduction in blood flow the partial pressure of oxygen in the synovial fluid of the rabbit knee joint was decreased during electrical stimulation of PAN (Ferrell and Najafipour 1992). Pharmacological studies performed using noradrenaline and appropriate antagonists have shown that these vasoconstrictor effects are probably mediated through alpha$_1$ and alpha$_2$ (mainly alpha$_1$) receptors but not by beta-receptors (Ferrell and Khoshbaton 1989, 1990).

V.B. Discharges in sympathetic units of joint nerves

Many postganglionic fibres in the joint nerve of cats knee are tonically active producing tonic vasoconstriction (Sato and Schaible 1987). They seem to exhibit a pattern of reflexes which is similar to that which has been observed in vasoconstrictor units of the skeletal muscle (Jänig 1985). It has been shown, for example, that (1) tonic activity exhibits fluctuations which are related to the inhibitory effect of baroreceptors, and (2) excitatory reflexes are evoked by noxious mechanical stimuli such as noxious movements in the knee and intra-articular injections of prostaglandins whereas in-

nocuous stimuli are ineffective (Sato and Schaible 1987).

V.C. Sympathetic activity during inflammation

In several sympathetic subsystems changes in efferent activity have been observed during the development of acute inflammation in joints. In the anaesthetized cat the heart rate and the sympathetic activity in cardiac postganglionic sympathetic neurones were found to increase during movements of the inflamed knee within the normal working range whereas noxious movements were required to elicit this reflex in normal animals (Sato et al. 1985, 1987). Increased reflex activity has also been described for the somatoadrenal reflexes (sympathetic adrenal nerve activity and adrenal catecholamine secretion) during joint inflammation (Sato et al. 1986). Surprisingly increases in the reflex discharges to the joint itself could not be found. In cats with normal and inflamed knee joints only noxious rotation of the knee against the resistance of the knee joint structures elicited a significant increase in the discharges of postganglionic efferent fibres in the joint nerve whereas innocuous movements in the knee did not produce any consistent effect (Sato and Schaible 1987). It could be postulated that the reflex discharges to the joint itself were 'relatively inhibited' during inflammation since there are significant increases in activity in other sympathetic subsystems. Insufficient data are available, however, on inflammation-induced changes in the sympathetic discharges in the efferent fibres to the joint to make firm statements at this time.

V.D. Sympathetic innervation and expression of inflammation

In a series of experiments a polyarthritis was induced in the rat by subdermal injection of *M. butyricum* into the tail, and additional pharmacological interventions were performed in order to investigate whether the activity of the nervous system would influence the progression and expression of the disease (Levine et al. 1986a, 1987; Coderre et al. 1990). Radiographic examination of the joints provided evidence that the action of the sympathetic nervous system enhanced the severity of the arthritis since (1) treatment

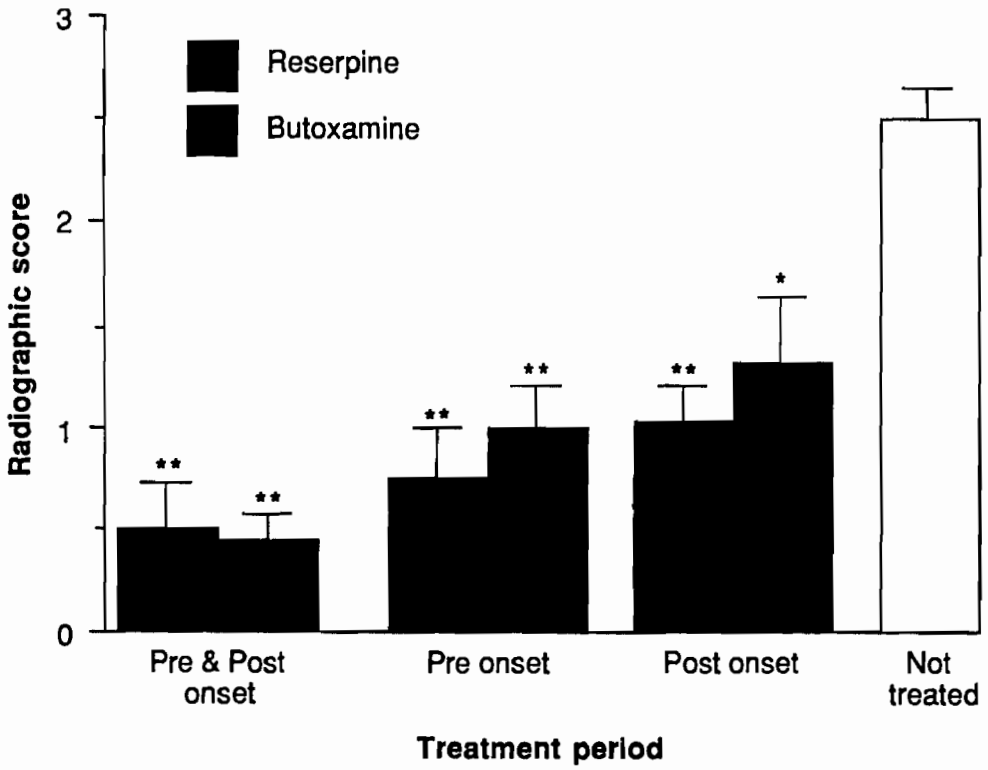

Fig. 12. Mean day-28 radiographic severity scores (±SEM) of adjuvant arthritic rats that were either untreated (open bar) or treated with reserpine (grey bars) or butoxamine (black bars) over treatment periods extending from (i) days −2 to 28 (pre- and postonset), (ii) either days −2 to 3 (reserpine) or days −2 to 8 (butoxamine) (preonset), or (iii) the first day clinical arthritis was detected to day 28 (postonset). The radiographs were scored for each hindpaw according to the 0–3 grading scale of Ackerman et al. (1979) taking into account soft-tissue swelling, decreased bone density, narrowing of the joint space, destruction of bone and formation of periosteal new bone. Chi-squared or Fisher's exact test comparisons were performed following a significant Kruskal-Wallis test statistic. Significant differences from the untreated group are indicated: * $P < 0.05$; ** $P < 0.01$). (Reproduced from Levine, J.D., Coderre, T.J., Helms, C. and Basbaum, A.I., Proc. Natl. Acad. Sci. USA, 85 (1988) 4553–4556, with permission from the authors.)

with reserpine or guanethidine (chemical sympathectomy) reduced the joint injury in the hindlimbs (Levine et al. 1986a, see Table II), (2) pretreatment with beta$_2$-adrenergic receptor antagonists retarded the disease onset and reduced the severity of the joint injury; this is shown in Fig. 12 which displays the inhibition of joint injury by treatment with reserpine and the selective beta$_2$-adrenergic antagonist butoxamine (given pre and/or postonset), and (3) adrenal medullectomy significantly reduced articular lesions suggesting adrenal medulla-derived epinephrine as the endogenous mediator involved (Coderre et al. 1990). As a mechanism the authors postulated that beta$_2$-antagonists were reducing the release of compounds from sympathetic postganglionic nerve terminals and also acted on cells of the immune system. In support of this they were unable to suppress symptoms of an arthritic lesion with beta$_1$-, alpha$_1$- or alpha$_2$-antagonists. The effect of epinephrine on the expression of joint injury was found, however, to be dose-dependent since only low doses of the compound enhanced joint injury whereas high doses decreased the severity of arthritic symptoms (Coderre et al. 1991). The reduction of arthritic symptoms induced by high doses was attributed to an action of epinephrine at the alpha$_2$-adrenergic receptor since it was antagonized by yohimbine and mimicked by the alpha$_2$-agonist clonidine (Coderre et al. 1991).

An aggravation of inflammatory symptoms by the sympathetic nervous system has not, however, been observed in other studies. Lam and Ferrell (1989a) were not able to induce a reduction in the severity (as judged by plasma extravasation) of the carrageenan-evoked acute arthritis in rat knees which had been pretreated for 3 days with reserpine to deplete sympathetic nerve endings of catecholamines. In the rat paw the neurogenic mustard oil inflammation and the non-neurogenic carrageenan oedema were not impaired after short-term chemical sympathectomy which resulted in a large (but incomplete) depletion of noradrenaline (Donnerer et al. 1991). It is not clear whether the time course of the inflammation (acute vs. chronic) or other factors (mode of induction of inflammation, etc.) are responsible for these differences.

There is also some evidence from studies in patients with rheumatoid arthritis that the sympathetic nervous system may control the severity of arthritic symptoms. Patients that underwent regional sympathetic blockade using guanethidine over 14 days described less pain and an increase in the pinch strength. The grip strength, tenderness and morning stiffness, however, were not significantly improved by guanethidine (Levine et al. 1986b). Another suggestion that the sympathetic nervous system may contribute to the severity of arthritic pain is the observation that there exist bilateral tissue abnormalities which include an inflammatory component in the joints of patients suffering from reflex sympathetic dystrophy, a condition where the efferent sympathetic outflow may be altered (Kozin et al. 1976).

V.E. Sympathetic innervation and plasma extravasation

Plasma extravasation results from the action of several chemical mediators released during the inflammatory process and allows rapid infiltration of immunocompetent cells into the damaged site. Evidence has been provided that the bradykinin-evoked plasma extravasation into the joint involves sympathetic postganglionic neurones since sympathectomy reduced plasma extravasation evoked by infusion of bradykinin into the knee joint of the rat whereas pretreatment with capsaicin did not attenuate this reaction (Coderre et al. 1989). The bradykinin-evoked plasma extravasation also seems to involve an action of polymorphonuclear leukocytes since depletion of these cells has been shown to reduce the bradykinin-evoked plasma extravasation (Bjerknes et al. 1991). It was proposed that bradykinin evoked the release of PGE_2 from sympathetic terminals (Gonzales et al. 1989) and thus activated polymorphonuclear leukocytes via an undefined mechanism that requires the sympathetic terminal (Bjerknes et al. 1991). Recently an interaction of bradykinin with the sympathetic terminals was shown via purinergic mechanisms since (1) ATP and adenosine were assumed to be co-transmitters with norepinephrine in the sympathetic postganglionic neurone and (2) the co-infusion of ATP or the adenosine A_2-receptor agonist 2-[4-(2-carboxyethyl)phenylethylamino]-5'-*N*-ethylcarboxamidoadenosine with bradykinin was shown to enhance the plasma extravasation (Green et al. 1991). On the other hand the application of ATP or adenosine reduced the severity of the radiographically assessed joint injury. On grounds of the opposing purinergic effects on plasma extravasation and joint injury it was suggested that enhanced plasma extravasation protects against joint injury (Green et al. 1991).

In summary the joints are supplied by efferent sympathetic nerve fibres which exhibit ongoing and reflex discharges in order to control the vascular tone (vasoconstrictor neurones). Several sympathetic subsystems such as the cardiac postganglionic sympathetic neurones and the sympathetic adrenal system show reflex discharges when noxious stimuli are applied to the joint and during acute inflammation of the joint this reflex activity seems to be increased. The sympathetic nervous system seems to contribute to the expression of the inflammatory lesions in the polyarthritic model since the reduction of sympathetic activity and/or the blockade of the postsynaptic effects by antagonists partially reduced the severity of the lesions. In acute experimental inflammation of the joint such an effect has not been found.

VI. Concluding remarks

The aim of neurobiological studies in pain research is to elucidate mechanisms of nociception and pain at acute and chronic stages of painful conditions and disorders. It is hoped that the understanding of the mechanisms involved in the sensitization of joint afferents, in the processing of neural information in the central nervous system and in processes of neuroplasticity in the peripheral and central nervous system will systematically reveal aspects of the pathways involved which can eventually be used for therapeutic intervention. Using the animal models of inflammation described in this review it has been possible to examine several aspects of the response of the nervous system to the development of an inflammatory lesion and these results demonstrate major patterns of reaction in the nervous system in the course of inflammation. This review did not address supraspinal mechanisms of nociception in joints although considerable information is available on neurones with joint input in thalamus and cortex. The reader is referred to the extensive work of Guilbaud and co-workers (see Guilbaud 1988). It should be noted that the studies investigating the function of the nervous system in arthritic conditions are only at an early stage although a large amount of data is already present. Major deficits in the understanding and contradictory results have been pointed out. Many other observations and conclusions may be challenged in future studies.

The authors believe that the continued use of animal models of inflammation in the joint will increase our understanding of the mechanisms involved in the signalling of arthritic pain. Still it has to be kept in mind that these animal models are only an approximation to human arthritic diseases and they may not take into account more specific factors depending on the particular aetiology and pathogenesis of the arthritis. The experimental work in animals, however, has provided many data on factors and mediators possibly involved and these could and should lead to related studies in humans. It could be asked, for example whether in different types and stages of arthritis (aetiology, pathogenesis, duration, etc.) particular inflammatory mediators in the periphery are predominant and whether under clinically relevant conditions only subsets and proportions of afferent fibres are activated and/or sensitized. In experimental inflammation at least, there is some evidence that inflammatory mediators may be preferentially produced and/or released at some stages of inflammation only (see Owen 1987; Salmon and Higgs 1987). The afferent fibres which are activated by the inflammatory mediators present may then determine which transmitters and neuromodulators are preferentially involved in the processing in the spinal cord.

Finally laboratory research should provide the clinician with options that can be used in the treatment of different types of joint pain in patients. Some antagonists acting at membrane receptors specific for many of the inflammatory mediators released in the periphery during inflammation are already under investigation as are antagonists working in different synaptic pathways in the spinal cord. The neurobiological data summarized in this review have, however, already shown that different inflammatory mediators, neurotransmitters and neuromodulators may be involved in the complex response of the nervous system and some may not have been even identified. It seems unlikely, therefore, that one standard approach or a single drug will be sufficient to suppress all types of pain in joints. There is hope, however, that experimental and clinical research will be able to define patterns of effective treatment for different types of joint pain.

Acknowledgements

The authors thank Dr. Volker Neugebauer for numerous suggestions and critical comments during the preparation of the manuscript, Mrs. M. Schulze and Mr. Colin Warwick for the preparation of the figures. During his stay in Würzburg Dr. Grubb was supported by the Deutsche Forschungsgemeinschaft.

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