MINIREVIEW

Functions of the Nociceptive Primary Neurons

Takao KUMAZAWA

*Department of Nervous and Sensory Functions,
Research Institute of Environmental Medicine,
Nagoya University, Nagoya, 464-01 Japan*

The most primitive nervous reflex is the "coiling reflex" observed in protochordates, that is, the coiling away of the animal body from a noxious stimulus. From the evolutionary point of view, all nervous regulation systems have been built upon the basis of this primitive withdrawal reflex. This also suggests the primitive but fundamental nature of the nociceptive system, as well as an intimate relationship between alarm and defense mechanisms.

Pain is divided into the so-called epicritic and protopathic types. The latter type is provided with complicated, intermingled systems of afferents and efferents. Recently the nature of the polymodal receptor, which belongs to the latter system, has been intensively studied. The receptor is characterized by great "wideness," both in terms of receptor characteristics and of the variety of bodily functions reflexively modulated by their input. Furthermore, even effector functions are provided at the endings of the sensory receptors, being mediated by the containing neuropeptides. The functions of nociceptive primary neurons are briefly reviewed herein with special reference to this recently delineated sensory receptor, the polymodal receptor.

NOCICEPTOR AND NON-NOCICEPTOR

Since the end of the last century, when pain was first classified as one of the sensory systems, there has been much contention between the specificity theory and the non-specificity or "intensity" theory, that is, whether pain has its own specific receptors and central pathways or not. In some ways, our daily experiences seem to support the "intensity" theory, which advocates that excessive stimulation to sensory receptors of any kind causes pain. However, experiments using single-unit recordings of thin-fiber afferents, started during the late 1960s, provided two important results supporting the specificity theory [5]. Firstly, arguing against the "intensity" theory, it was shown that the discharge of non-nociceptors does not increase when the intensity of a stimulus increases above a noxious range, on one

Fig. 1. Diagrammatic representation of stimulus intensity-response relationships of 2 types of nociceptors (①, ②) and non-nociceptors (③).

hand (Fig. 1, ③). Secondly, on the other hand, confirming the specificity of the nociceptor, a certain type of sensory receptors could respond to noxious stimuli in an intensity-dependent manner (Fig. 1, ①).

The term nociceptor is derived from Sherrington's definition: the sensory receptors which respond to noxious stimuli of a nature or an intensity that threatens to damage tissue. Several types of nociceptors have been proposed by different investigators.

As shown in Fig. 1, nociceptors may be divided into two groups: one responds almost exclusively to stimulation in the noxious range (Fig. 1, ①), whereas the other not only increases the discharge-rates intensity-dependently within the noxious range, but also responds to non-noxious stimuli (Fig. 1, ②). The high-threshold mechanoreceptor [4] belongs to the former group, and the polymodal receptor [1, 32] to the latter one.

NOCICEPTIVE PRIMARY AFFERENT NERVES

It has long been known that pain is transmitted by small afferent nerve fibers, namely, either unmyelinated (C) or small myelinated (A-delta) fibers. In fact, the type of afferent nerve fibers tends to differ depending on the type of sensory receptors they innervate, but the difference is not absolute. The activities of non-nociceptors, such as thermoreceptors, down-hair receptors, and so on, are also conducted by small afferent fibers; a type of receptor that is innervated by C fibers in small animals may be innervated by A fibers in large animals; and it is not unusual for

a single afferent fiber to be composed of A fiber in its proximal section and C fiber in the distal section [25].

The cell bodies of these somatic and visceral nociceptive afferent fibers are located in the spinal dorsal root ganglia (DRG). However, some of the vagal nodosa ganglion cells are also presumed to be concerned with nociception, since algescic substances such as bradykinin (BK) excite these cells [12]. Nociceptive visceral afferents running along the sympathetic nerves pass through the sympathetic ganglia, while giving rise to collateral fibers which make synaptic contacts with some of the ganglion cells.

The cell body of these small fiber afferents tends to have the smallest size of the entire DRG cells population. However, relatively large cells are found among these originating C fiber afferents. This may be related in part to the fact that these cells produce neuropeptides, as will be discussed later.

As stated in the classical law of Bell-Magendie, the dorsal roots are purely sensory. However, not all ventral root fibers are efferent; approximately 30% of C fibers in the ventral roots are found to be afferent fibers presumably of nociceptive function [8]. Dichotomized innervation of single DRG cells into the skin and viscera has been known in frog and fish; and recently the double fluorescence marking method revealed the existence of dichotomized DRG cell in mammals [45], though the number of cells of this type is too small to explain referred pain.

Nociceptive afferent fibers enter the spinal cord through the lateral portion of the dorsal root [36], and run further rostrally and caudally through the Lissauer tract and at the dorsolateral edge of the dorsal horn. The spinal gray matter is divided into 10 layers according to the cytoarchitectonic organization (Rexed, 1952). Marginal cells in the dorsalmost lamina I receive inputs exclusively from the high-threshold mechanoreceptors [7, 33]. Cutaneous C fiber polymodal receptors end in the lamina II cells [33, 48], which project to the thalamus not directly but through the wide dynamic range neurons that receive inputs from low- as well as high-threshold receptors. C fiber afferents from the viscera are also distributed in several segments rostral and caudal to the entry zone. A few branchings end in lamina II, but the great majority of them end in laminae I and V (our unpublished data). This wide expansion of spinal endings of C fiber DRG cells may also explain the relatively large size of the soma of these neurons. Electrophysiological findings reveal that dorsal horn neurons with inputs from deep tissues always have cutaneous inputs as well, indicating the basis for convergence theory of referred pain [6].

HIGH-THRESHOLD MECHANORECEPTOR

Under normal conditions, the high-threshold mechanoreceptors in the skin respond only to noxious mechanical stimuli, but not to either chemical or heat stimuli. Discharges are evoked in a limited fashion only during the period of stimulus application [4]. After the repeated application of strong heat stimuli, however, the receptor becomes sensitive to heat stimulation. The results of studies on human

pain sensation and on discharges of high-threshold mechanoreceptor units in monkeys, both of which are tested using the same method of repetitive heat stimulation, strongly suggest that hyperalgesia suffered as a burning is caused by the activity of this receptor [37].

The receptive field of this receptor is round or elliptical of 1 to 8 cm² size, and contains 3 to 6 sensitive spots within it. Electron microscopic examination of these sensitive spots, identified electrophysiologically, has revealed that unmyelinated endings accompanied by thin Schwann cell processes penetrate the epidermal basal lamina in the papillae, being surrounded by keratinocytes [20]. Existence of the Schwann sheath as well as keratinocytes may explain the purely mechanonociceptive characteristics of the receptor under the normal conditions.

This type of receptor occupies 15 to 25% of the A-delta fiber receptors in the skin of cats and monkeys, but is quite rare or nonexistent in the deep tissues. The secondary neurons of this receptor in the lamina I layer project through the spino-thalamic tract to the specific thalamic nuclei [7, 33]. Therefore, the receptor is considered to be responsible for signaling of discriminative pain, such as prick pain from the skin.

POLYMODAL RECEPTOR

It is common for the sensitivity of sensory receptors to be limited to a certain type of stimulus. Polymodal receptors, however, are characterized by their responsiveness to a wide variety of stimulus types, including mechanical, chemical, and heat stimuli (Fig. 2).

It is from this characteristic that the term "polymodal" is derived. Polymodal receptors are found in the skin as well as in somatic and visceral deep tissues [1, 22, 25, 32], and are thus characterized by a wide distribution throughout the body. To these features we may add the wide dynamic range, an ability to respond to a wide range of stimulus intensity, mentioned above. These three "wide-nesses" characterize the activity of the receptor. The population of polymodal receptors in the entire population of cutaneous C fiber afferents is 34 to 40% in cats, 85 to 90% in monkeys, and nearly 100% in humans. A large number of A fiber polymodal receptors is found in the deep tissues [22, 25, 28].

The receptive field of this receptor is spot-like, and only 1 mm² in size. One single fiber corresponds to one spot in the skin [1, 32], but usually to several spots in the viscera [25]. Electron microscopic examination of the identified spots shows the endings to be surrounded by a thin layer of Schwann cell cytoplasm and packed with a variety of organelles, including mitochondria, a few round spherical vesicles, and numerous membrane-bound dense bodies [19]. The result indicating no synaptic contact with special receptor structure fits with the neurophysiological data on the response of the receptor to changes in concentration ratio of Ca and Mg ions in the milieu [47].

A slowly adapting response is evoked intensity-dependently by mechanical

Fig. 2. Response patterns of polymodal receptors in the deep tissues. Top traces, responses to mechanical stimulation of 2 intensities (in A, the receptive spot was pressed using a strain gauge-mechanostimulator with a tip diameter of 0.75 mm and in B, a weight of 500 or 1,000 g was applied on the testis using a mechanostimulator with a tip diameter of 10 mm); middle traces, peristimulus histograms of discharge responses to application of bradykinin (1 μ g/ml), indicated by BK at the lower bar deflexion (in A, by close-arterial injection and in B, by applying a cotton ball 1.5 mm in diameter soaked with the solution on a receptive site); bottom traces, responses to radiant heat.

stimulation, which is applied exactly on the receptive spot. After-discharges are commonly observed with stimulation within the noxious range [25].

Heat stimulation above around 45°C evokes irregular but intensity-dependent discharges. Heating of several °C above the threshold temperature augments the subsequent responses to heat as well as to algescic substances, indicating "sensitization" of the receptor [27]. Further excessive heat stimulation causes the response to the subsequent heating of the same intensity to decrease [22, 25, 32], while the sensitization of the responses to heating at lower temperatures and to algescic substances is preserved in such conditions [27].

It has been revealed in somatic [22] as well as in visceral polymodal receptors [24, 28] that BK, high concentration of KCl, and hypertonic saline applied to the receptive field evoke discharges in a consistent and dose-dependent fashion, whereas they are ineffective if applied on the nerve trunk. BK is the most conceivable

endogenous pain substance, and a high concentration of KCl is expected to be released from injured cells. The effective concentrations of both these substances applied experimentally are within the range appearing in injured tissues. The response to BK is suppressed by an antagonist of B₂ type, but not affected by that of B₁ type. Therefore, of the 2 types of BK receptor [46], the BK response of the polymodal receptor is mediated by the B₂ type [39]. Histamine and acetylcholine cause far less of a response than BK does; substance P (SP), a neuropeptide found in the thin-fiber primary afferents mentioned later, is effective neither to activate nor to sensitize the receptor [23].

MODULATION OF POLYMODAL RECEPTOR ACTIVITIES

Another characteristic of the responses of polymodal receptors is a limited reproducibility, such as the "heat sensitization" mentioned above, suggesting the role of this receptor in signaling the changes caused by noxious or tissue-damaging stimuli. The activities of the receptor are easily modulated by various processes presumed to occur in the microenvironment of the receptor site.

The levels of several types of prostaglandin (PG) and serotonin (5-HT) are known to increase in damaged or inflamed tissues. PGE₂, PGI₂, and 5-HT do not consistently elicit discharges of polymodal receptors at a concentration at which BK does cause strong responses. However, responses to BK as well as heat are enhanced by these substances at concentrations two-orders lower than those necessary for the substances alone to evoke discharges [30, 40]. Responses to heat are also enhanced by BK at a low concentration at which BK *per se* does not induce discharges.

The response to BK but not to hypertonic saline is remarkably suppressed by aspirin or indomethacin, cyclo-oxygenase inhibitors; and this effect is reversed by PGE₂ [24, 27, 30, 40]. This reveals an involvement of PGs in the response to BK, since BK is known to stimulate PG synthesis through activation of phospholipase A₂ [10].

While the analgesic effects of opioids have long been known to be induced by their central action, peripheral analgesic effects of opioids have also been reported using behavioral analgesic tests on inflamed tissues [9]. However, opioids do not have an inhibitory effect on the activities of polymodal receptors. Rather, a significant and naloxone-reversible enhancement of the response to BK is produced [31]. The cause of this discrepancy has not yet been resolved; however, it is presumed that peripheral opioid effects are not directly related to the nociceptor activity, but depend instead on the modulation of processes related to development of inflammation.

Cooling an inflamed region alleviates spontaneous pain, while warming intensifies it. If the polymodal receptor is involved in the signaling of inflammatory pain, then the thermal effects on inflammatory pain should be simulated when the polymodal receptor is thermally stimulated, though the threshold temperature of

this receptor is much higher than that expected in inflamed tissues (calor). Confirming the ordinary experiences, responses to hypertonic saline as well as to BK are monotonously augmented by heating to between 30 and 43°C, which alone proves to be a subthreshold stimulus for the polymodal receptor [29, 30].

Changes in ionic milieu also modulate the responses of polymodal receptors [30, 47]. Reducing the extracellular concentration of K^+ decreases the response to BK, whereas increasing it causes the opposite effect, as expected. When the concentration of K^+ is reduced to 0, there is an increase in spontaneous discharges, which are suppressed by cooling and increased by warming, and an augmentation of the responses to hypertonic saline. This might be caused by the suppression of the electrogenic Na^+-K^+ pump activity, since ouabain simulates this effect. The responses to hypertonic saline and high K^+ are enhanced under the extracellular Ca^{2+} -free condition: and this effect is reversed by the addition of excess Mg^{2+} , indicating the intervention of Ca^{2+} -dependent "membrane surface potential." On the contrary, responses to BK are reduced by the absence of Ca^{2+} . The mechanisms of this phenomenon have not yet been clarified. The effect of this absence on Ca^{2+} -dependent phospholipase A_2 mediating PG synthesis may not be the main cause, since the suppression of responses to BK under the Ca^{2+} -free condition is not effectively reversed by application of PGE_2 .

Exposure to clioquinol, which is known as a causal agent of subacute myelo-optico-neuropathy (SMON), induces abnormal intermittent bursting activities in polymodal receptors, as well as a new sensitivity to cold. It also enhances their responsiveness to hypertonic saline [26].

CAPSAICIN AND NEUROPEPTIDES

When a low concentration of capsaicin, a pungent component of red peppers, is applied to human skin, a burning pain is elicited and the pain threshold is lowered. After pretreatment with a high concentration of capsaicin, however, pain is reduced or abolished without affecting touch or pressure sensations. Capsaicin causes the release of neuropeptides from the central and peripheral terminals of the primary nociceptive afferents, resulting in their depletion. Pretreatment with a high concentration of capsaicin in animals causes selective degeneration of thin-fiber primary afferent neurons. These morphological changes appear within only 2 to 6 h after the application. They are permanent in animals treated neonatally, and last for several days to 1 month in adult animals. This effect of capsaicin has led to a search for a method of selective chemical denervation of pain fibers [16].

Many kinds of peptides, such as tachykinin, somatostatin, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide, and so on, have been found singly or in coexistence in primary afferent neurons with thin-fibers [13]. The action of SP, the first of these peptides to be found and synthesized, has been studied extensively. The following findings strongly suggest that SP has a transmitter-like action in the spinal pain-signaling system: 1) a dense immuno-

reactive SP of dorsal root origin is found in the superficial laminae of dorsal horn [14]; 2) the stimulation of thin-fiber afferents or application of capsaicin increases SP levels in the superfusate or perfusate of the spinal cord, this release of SP being naloxone-reversibly inhibited by opioids [42, 50]; 3) a microinjection of SP in the spinal cord lowers the pain threshold [11]; 4) the nociceptive depolarizing responses recorded in the ventral root are depressed by an SP antagonist [43]; 5) a significant increase in the biosynthesis of SP-related substances in the DRG, expressed by preprotachykinin mRNA levels, is induced by noxious stimuli [41]. Other neuropeptides like somatostatin have also been reported to play roles in spinal nociceptive transmission [35].

The role of the nerve growth factor (NGF) in the biosynthesis of these neuropeptides, and hence in the development and function of peptidergic sensory neurons, is strongly suggested [44]. NGF dose-dependently increases neuropeptides in DRG and in the spinal cord, while NGF-antibodies reduces them, together with nociceptive responses. Furthermore, intrauterine injection of NGF-antiserum results in a remarkable loss of thin-fiber dorsal root fibers. The neurotoxic effects of capsaicin are antagonized by NGF, suggesting that the effects of capsaicin depend on the suppression of uptake and/or transport of NGF from the periphery.

NEUROGENIC INFLAMMATION

Since a 100 years ago, it has been known that dorsal root stimulation causes inflammation-like vascular changes in the innervating peripheral area through an axon reflex. Flare in injured tissues is a sign of such neurogenic inflammation. The following findings indicate that neurogenic inflammation is caused by the activation of nociceptive afferent fibers: 1) the flare reaction is induced by noxious stimuli; 2) the intensity of antidromic dorsal root stimulation is above the threshold for unmyelinated fibers; 3) capsaicin pretreatment prevents neurogenic inflammation, and also reduces sensitivity to pain [49]; and 4) the antidromic single-fiber stimulation of C fibers, identified as polymodal receptors, elicits extravasation at the receptive site of the receptor, a reaction not observed in other types of non-nociceptor C fibers [17].

Neuropeptides released from the thin-fiber afferent terminals are the first-step mediators of the neurogenic inflammation, as can be deduced from the facts that 1) antidromic stimulation of these afferents causes the release of neuropeptides at the innervated area [3]; 2) intra-arterial injection of these peptides causes signs of neurogenic inflammation; and 3) antagonists of these peptides suppress neurogenic inflammation [15]. Vascular reactions, caused either by antidromic stimulation or by application of SP, are suppressed by SP antagonists and also by antagonists as well as depletors of histamine, suggesting implication of an SP-activated histamine release from the mast cells located near sensory nerve endings. One argument against this notion, however, is that flare responses to capsaicin are not inhibited by histamine antagonists.

Fig. 3. Various local regulatory effects mediated by neuropeptides. 1-10, target cells.
* Neuropeptides and their precursors.

As shown in Fig. 3, various peripheral functions other than vascular reactions are known to be regulated by neuropeptides, such as chemotaxis and phagocytosis of macrophages and polymorphonuclear leukocytes; the production of arachidonate metabolites and immunoglobulins; the proliferation of T-lymphocytes and fibroblasts; the activities of non-vascular smooth muscles and cardiac muscles; the activities of autonomic ganglia, and so on.

Thus, though the actions of various neuropeptides differ among tissues as well as between species, it is clear that the effector functions of peripheral nociceptive neurons are not limited to inflammatory reactions but involve influences on the immune system; on the contraction or relaxation of non-vascular smooth muscles in the eye, the respiratory, urogenital, and gastrointestinal tracts; on the cardiac muscles; on the facilitation of wound healing; as well as on the regulation in the autonomic ganglia.

When one takes into account the facts that more than 95% of SP synthesized in the DRG is transported to the peripheral fibers of sensory neurons rather than to their central axons [2] and that many kinds of peptides exist in the thin-fiber afferent terminals, it would seem that the roles of these peptides and thus the roles of the thin-fiber afferents in the local regulation of peripheral functions are more important than has hitherto been considered.

THE ROLES OF NOCICEPTORS AS REFLEX AFFERENTS

As would be easily noted from the term "pseudo-affective reflexes," nociceptor activities causes profound effects on a number of bodily functions. Little importance has been attached to this aspect of pain; however, this should not be ignored. It is quite natural that an organism's "alarm system" should be intimately connected to its "defense system." This organization is to the organism's advantage in an emergency; however, it produces stress on bodily functions which may even be harmful after an extended period. The reflexive effects of the nociceptor activities are thus something of a double-edged sword, and should therefore be studied more intensively.

Another point which merits our attention is the wide dynamic range of the polymodal receptors; that is, their responsiveness to non-noxious as well as noxious stimuli. KHAYUTIN *et al.* [18] have differentiated two components, one non-nociceptive and the other nociceptive, of the response of blood pressure to the intra-arterial injection of BK to the visceral area. Our result [24] on the single-unit discharges of the testicular polymodal receptor responding to BK shows a dose relationship similar to that observed in reflex responses to BK in the same concentration range, indicating the implication of polymodal receptors in both, the non-nociceptive and nociceptive components of the responses. Reflexive augmentation of respiration is also elicited by muscular polymodal receptor inputs [38]. If the stimulus is strong enough this augmentation is followed by a suppression of respiration, which is mediated by endogenous opioid system [34]. A negative feedback

mechanism involving endogenous opioids triggered by polymodal receptor inputs is also presumed in the analgesic mechanisms of acupuncture [21]. These findings strongly suggest an intimate relationship between fundamental bodily functions and the polymodal receptor, a primitive sensory receptor.

SUMMARY

The functions of nociceptive primary neurons are reviewed in brief, with special reference to the polymodal receptor. The polymodal receptor is considered to be a primitive sensory receptor that is not well differentiated and that plays important roles in signaling pain especially from tissues in pathological states, and in causing reflex modulations of a wide variety of bodily functions. This sensory receptor is characterized by the existence of neuropeptides in its neuron. The wide distribution of the central axon branchings of this neuron and the long-lasting effects of the neuropeptides released from the axon terminals provide an "analogue-like" action of the nervous system, which had hitherto been considered to be "digital-like," point-to-point connections in the central neuron network. Neuropeptides released from the peripheral endings of this neuron, on the other hand, play important roles in local regulation of such functions as inflammation, visceral tract motility, trophic effects, immune system functioning and so on.

The functions of nociceptive primary neurons are, therefore, not limited to sensory function but should be understood as a component related to the regulation of fundamental functions of the entire organism.

Key words: nociceptor, polymodal receptor, neuropeptide, inflammation, autonomic reflex.

The works from the author's laboratory cited in this review were supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1. BESSOU, P. and PERL, E. R. (1969) Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J. Neurophysiol.*, **32**: 1025-1043.
2. BRIMJOIN, S., LUNDBERG, J. M., BRODIN, E., HÖKFELT, T., and NILSSON, G. (1980) Axonal transport of substance P in the vagus and sciatic nerves of the guinea pig. *Brain Res.*, **191**: 443-457.
3. BRODIN, E., GAZELIUS, B., PANOPOULOS, P., and OLGART, L. (1983) Morphine inhibits substance P release from peripheral sensory nerve endings. *Acta Physiol. Scand.*, **117**: 567-570.
4. BURGESS, P. R. and PERL, E. R. (1967) Myelinated afferent fibres responding specifically to noxious stimulation of the skin. *J. Physiol. (Lond.)*, **190**: 541-562.
5. BURGESS, P. R. and PERL, E. R. (1973) Cutaneous mechanoreceptors and nociceptors. In: *Handbook of Sensory Physiology. II. Somatosensory System*, ed. by IGGO, A.,

- Springer, Berlin, pp. 27–78.
6. CERVERO, F. and TATTERSALL, J. E. H. (1986) Somatic and visceral sensory integration in the thoracic spinal cord. *In: Progress in Brain Research*, ed. by CERVERO, F. and MORRISON, J. F. B., Elsevier Publ. Co., Amsterdam, Vol. 67, pp. 189–205.
  7. CHRISTENSEN, B. N. and PERL, E. R. (1979) Spinal neurons specifically excited by noxious or thermal stimuli: Marginal zone of the dorsal horn. *J. Neurophysiol.*, **33**: 293–307.
  8. COGGESHALL, R. E., MAYNARD, C. W., and LANGFORD, L. A. (1980) Unmyelinated sensory and preganglionic fibers in rat L₆ and S₁ ventral spinal roots. *J. Comp. Neurol.*, **193**: 41–47.
  9. FERREIRA, S. H. and NAKAMURA, M. (1979) II-Prostaglandin hyperalgesia: The peripheral analgesic activity of morphine, enkephalins and opioid antagonists. *Prostaglandins*, **18**: 191–200.
  10. FLOWER, R. J. and BLACKWELL, G. J. (1976) The importance of phospholipase-A₂ in prostaglandin biosynthesis. *Biochem. Pharmacol.*, **25**: 285–291.
  11. HAYES, A. G. and TYERS, M. B. (1979) Effects of intrathecal and intracerebroventricular injections of substance P on nociception in the rat and mouse. *Br. J. Pharmacol.*, **66**: 488.
  12. HIGASHI, H. (1986) Pharmacological aspects of visceral sensory receptors. *In: Progress in Brain Research*, ed. by CERVERO, F. and MORRISON, J. F. B., Elsevier Publ. Co., Amsterdam, Vol. 67, pp. 149–162.
  13. HÖKFELT, T., JOHANSSON, O., LJUNGDAHL, Å., LUNDBERG, J. M., and SCHULTZBERG, M. (1980) Peptidergic neurones. *Nature*, **284**: 515–521.
  14. HÖKFELT, T., KELLERTH, J. O., NILSSON, G., and PERNOW, B. (1975) Experimental immunohistochemical studies on the localization and distribution of substance P in cat primary sensory neurons. *Brain Res.*, **100**: 235–252.
  15. HOLZER, P. (1988) Local effector functions of capsaicin-sensitive sensory nerve endings: Involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience*, **24**: 739–768.
  16. JANCsó, G., KIRÁLY, E., SUCH, G., JOó, F., and NAGY, A. (1987) Neurotoxic effect of capsaicin in mammals. *Acta Physiol. Hung.*, **69**: 295–313.
  17. KENINS, P. (1981) Identification of the unmyelinated sensory nerves which evoke plasma extravasation in response to antidromic stimulation. *Neurosci. Lett.*, **25**: 137–141.
  18. KHAYUTIN, V. M., BARAZ, L. A., LUKOSHKOVA, E. V., SONINA, R. S., and CHERNILOVSKAYA, P. E. (1976) Chemosensitive spinal afferents: Thresholds of specific and nociceptive reflexes as compared with thresholds of excitation for receptors and axons. *In: Progress in Brain Research*, ed. by IGGO, A. and ILYINSKY, O. B., Elsevier Publ. Co., Amsterdam, Vol. 43, pp. 293–306.
  19. KRUGER, L., KUMAZAWA, T., MIZUMURA, K., SATO, J., and YEH, Y. (1988) Observations on electrophysiologically characterized receptive fields of thin testicular afferent axons: A preliminary note on the analysis of fine structural specializations of polymodal receptors. *Somatosens. Res.*, **5**: 373–380.
  20. KRUGER, L., PERL, E. R., and SEDIVEC, M. J. (1981) Fine structure of myelinated mechanical nociceptor endings in cat hairy skin. *J. Comp. Neurol.*, **198**: 137–154.
  21. KUMAZAWA, T. (1978) On the mechanisms of “acupuncture anesthesia”—1. Is “acupuncture anesthesia” effective? What is the afferent mechanism?—. *Clin. Physiol.*, **8**: 413–419 (in Japanese).

22. KUMAZAWA, T. and MIZUMURA, K. (1977) Thin-fibre receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. *J. Physiol. (Lond.)*, **273**: 179–194.
23. KUMAZAWA, T. and MIZUMURA, K. (1979) Effects of synthetic substance P on unit-discharges of testicular nociceptors of dogs. *Brain Res.*, **170**: 553–557.
24. KUMAZAWA, T. and MIZUMURA, K. (1980) Chemical responses of polymodal receptors of the scrotal contents in dogs. *J. Physiol. (Lond.)*, **299**: 219–231.
25. KUMAZAWA, T. and MIZUMURA, K. (1980) Mechanical and thermal responses of polymodal receptors recorded from the superior spermatic nerve of dogs. *J. Physiol. (Lond.)*, **299**: 233–245.
26. KUMAZAWA, T. and MIZUMURA, K. (1984) Abnormal activity of polymodal receptors induced by clioquinol (5-chloro-7-iodo-8-hydroxyquinoline). *Brain Res.*, **310**: 185–188.
27. KUMAZAWA, T., MIZUMURA, K., and SATO, J. (1987) Modulations of testicular polymodal receptor activity: Implication of receptors in inflammatory pain. In: *Fine Afferent Nerve Fibers and Pain*, ed. by SCHMIDT, R. F., SCHAIKLE, H.-G., and Vahle-Hinz, C., VCH Verlagsgesellschaft mbH, Weinheim, pp. 147–157.
28. KUMAZAWA, T., MIZUMURA, K., and SATO, J. (1987) Response properties of polymodal receptors studied using *in vitro* testis superior spermatic nerve preparations of dogs. *J. Neurophysiol.*, **57**: 702–711.
29. KUMAZAWA, T., MIZUMURA, K., and SATO, J. (1987) Thermally potentiated responses to algescic substances of visceral nociceptors. *Pain*, **28**: 255–264.
30. KUMAZAWA, T., MIZUMURA, K., and SATO, J. (1988) Modulation of testicular polymodal receptor activities. In: *Progress in Brain Research*, ed. by HAMANN, W. and IGGO, A., Elsevier Publ. Co., Amsterdam, Vol. 74, pp. 325–330.
31. KUMAZAWA, T., Mizumura, K., SATO, J., and MINAGAWA, M. (1989) Facilitatory effects of opioids on the discharges of visceral nociceptors. *Brain Res.*, **497**: 231–238.
32. KUMAZAWA, T. and PERL, E. R. (1977) Primate cutaneous sensory units with unmyelinated (C) afferent fibers. *J. Neurophysiol.*, **40**: 1325–1338.
33. KUMAZAWA, T. and PERL, E. R. (1978) Excitation of marginal and substantia gelatinosa neurons in the primate spinal cord: Indications of their place in dorsal horn functional organization. *J. Comp. Neurol.*, **177**: 417–434.
34. KUMAZAWA, T., TADAKI, E., and KIM, K. (1980) A possible participation of endogenous opiates in respiratory reflexes induced by thin-fiber muscular afferents. *Brain Res.*, **199**: 244–248.
35. KURAISHI, Y., HIROTA, N., SATO, Y., HINO, Y., SATOH, M., and TAKAGI, H. (1985) Evidence that substance P and somatostatin transmit separate information related to pain in the spinal dorsal horn. *Brain Res.*, **325**: 294–298.
36. LIGHT, A. R. and PERL, E. R. (1979) Reexamination of the dorsal root projection to the spinal dorsal horn including observations on the differential termination of coarse and fine fibers. *J. Comp. Neurol.*, **186**: 117–131.
37. MEYER, R. A. and CAMPBELL, J. N. (1981) Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. *Science*, **213**: 1527–1529.
38. MIZUMURA, K. and KUMAZAWA, T. (1976) Reflex respiratory response induced by chemical stimulation of muscle afferents. *Brain Res.*, **109**: 402–406.
39. MIZUMURA, K., MINAGAWA, M., TSUJII, Y., and KUMAZAWA, T. (1990) The effects of bradykinin agonists and antagonists on visceral polymodal receptor activities. *Pain*, **40**: 221–227.
40. MIZUMURA, K., SATO, J., and KUMAZAWA, T. (1987) Effects of prostaglandins and

- other putative chemical intermediaries on the activity of canine testicular polymodal receptors studied *in vitro*. *Pflügers Arch.*, **408**: 565-572.
41. NOGUCHI, K., MORITA, Y., KIYAMA, H., ONO, K., and TOHYAMA, M. (1988) A noxious stimulus induces the preprotachykinin-A gene expression in the rat dorsal root ganglion: A quantitative study using *in situ* hybridization histochemistry. *Mol. Brain Res.*, **4**: 31-35.
  42. OTSUKA, M. and KONISHI, S. (1976) Release of substance P-like immunoreactivity from isolated spinal cord of newborn rat. *Nature*, **264**: 83-84.
  43. OTSUKA, M. and YANAGISAWA, M. (1988) Effect of a tachykinin antagonist on a nociceptive reflex in the isolated spinal cord-tail preparation of the newborn rat. *J. Physiol. (Lond.)*, **395**: 255-270.
  44. OTTEN, U. (1984) Nerve growth factor and the peptidergic sensory neurons. *Trends Pharmacol. Sci.*, **5**: 307-310.
  45. PIERAU, F.-K., FELLMER, G., and TAYLOR, D. C. M. (1984) Somato-visceral convergence in cat dorsal root ganglion neurones demonstrated by double-labelling with fluorescent tracers. *Brain Res.*, **321**: 63-70.
  46. REGOLI, D. and BARABÉ, J. (1980) Pharmacology of bradykinin and related kinins. *Pharmacol. Rev.*, **32**: 1-46.
  47. SATO, J., MIZUMURA, K., and KUMAZAWA, T. (1989) Effects of ionic calcium on the responses of canine testicular polymodal receptors to algesic substances. *J. Neurophysiol.*, **62**: 119-125.
  48. SUGIURA, Y., LEE, C. L., and PERL, E. R. (1986) Central projections of identified, unmyelinated (C) afferent fibers innervating mammalian skin. *Science*, **234**: 358-361.
  49. SZOLCSÁNYI, J. (1988) Antidromic vasodilatation and neurogenic inflammation. *Agent. Actions*, **23**: 4-11.
  50. YAKSH, T. L., JESSELL, T. M., GAMSE, R., MUDGE, A. W., and LEEMAN, S. E. (1980) Intrathecal morphine inhibits substance P release from mammalian spinal cord *in vivo*. *Nature*, **286**: 155-157.