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Understanding the neurophysiology of pain syndromes facilitates the optional management of cancer-related pain.

Neurophysiology of Cancer Pain

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Background: *Recent basic science research has greatly added to our knowledge of pain mechanisms. Application of this knowledge to cancer pain syndromes has led to new and innovative approaches to cancer pain management.*

Methods: *The mechanisms involved in the three main cancer pain syndromes (somatic, visceral, and neuropathic) are reviewed, and various therapeutic options are discussed.*

Results: *Advances in knowledge in neurophysiology, neuroanatomy, and pharmacology have allowed a greater understanding of the peripheral and central mechanisms of pain. New drugs and interventional techniques based on this knowledge have improved the control of cancer pain.*

Conclusions: *Understanding the neurophysiology of cancer pain promotes use of the most appropriate palliative measures for pain control.*

Introduction

It is estimated that 70% to 90% of patients with advanced cancer experience significant pain. Since uncontrolled pain can have an adverse impact on patients and their families, optimal management of pain should be a priority goal for all clinicians.¹⁻³

Cancer pain syndromes can be classified as somatic, visceral, or neuropathic in origin. Pain may be due to

tumor infiltration of local structures or to antineoplastic therapy, or it may be unrelated to the tumor.² Recognition of pain syndromes is essential for the adequate management of cancer pain. Basic science research on the mechanisms of pain has been helpful in providing the scientific rationale for new approaches to cancer pain management. This article reviews the neurophysiology of pain, with an emphasis on the understanding and treatment of cancer pain syndromes.

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Pain Anatomy and Physiology

Nociceptor

Nociceptors are specialized terminal peripheral branches of sensory nerve fibers that are sensitive to noxious stimuli. C-polymodal receptors with unmyeli-

nated afferent axons respond to a variety of noxious stimuli such as mechanical and thermal stress or chemicals released from damaged, inflamed skin.⁴ A δ mechanoreceptors are normally responsive to intense mechanical stimuli, but they can be sensitized by noxious heat.⁵ Pain from skin, muscles, and joints is evoked by a variety of mechanical, chemical, and thermal stimuli and is mediated by somatic nerves, resulting in a clearly perceived and well-localized sensation. Pain from viscera is evoked by ischemia, spasm, or inflammation of smooth muscle as well as mechanical stimulation such as distension of the mesentery. Visceral nociceptive fibers run in sympathetic and parasympathetic nerves, and the pain evoked by the activation of these fibers has no precise location.

The role of the peripheral component of primary afferent neurons has long been considered limited to nociception activation and transduction of sensory input. Recently, its role also expanded to modulation and integration of nociceptive input.⁶ Following tissue injury, chemical mediators or ligands of nociceptor origin (substance P, cholecystokinin) or from non-neuronal sources (acetylcholine, prostaglandin, bradykinin) are released to the vicinity of nociceptors that may be activated and sensitized. Many nociceptors are inactive or "silent" under normal circumstances. They are activated and recruited only under pathological conditions such as inflammation. The resultant "soup" of chemical mediators also changes the transduction sensitivity of nociceptors, resulting in reduction of threshold for activation and increased response to suprathreshold stimulus, ie, peripheral sensitization.

Spinal Cord

The cell bodies of primary afferent fibers are located in the dorsal root ganglion and give rise to axons that enter the spinal cord through the dorsal root. The axon of the A δ and C fibers may ascend or descend as much as three levels before entering the dorsal horn. The cytoarchitecture of the spinal gray matter was defined by Rexed into 10 lamina, and the first six make up the dorsal horn. C fibers terminate almost exclusively in lamina I and II, while A δ fibers terminate in both the superficial and deep lamina of the dorsal horn. Lamina II, the substantia gelatinosa, is the zone where dense terminations of C and A δ fibers are found and where the majority of the transmitters and receptors are concentrated. Therefore, it is considered the primary site of nociceptive afferent processing. In the dorsal horn, neurons sending off ascending fibers to the higher center are subject to the influence of interneurons in the local circuitry and the descending fibers from the higher center.

There are two major classes of neurons in the dorsal horn responding to nociceptive stimuli. Nociceptive-specific neurons, responding only to noxious stimuli, are most abundant in superficial lamina and their receptor fields are discrete and vary from one to several square centimeters. However, the ability of these neurons to encode the intensity of noxious stimuli is weak. Wide dynamic range (WDR) neurons in contrast, respond to a wide range of stimuli from A δ , A β , and C fibers in a graded manner (ie, the rate of firing escalates with increasing intensity of stimulation). WDR neurons can be found in all lamina and are the most prevalent cells in the dorsal horn. Because of their unique response to innocuous or nociceptive input as well as their larger receptor field, WDR neurons play an important role in the central sensitization and the plasticity of the spinal cord.

Central Sensitization

Normally, noxious stimuli carried through peripheral A δ and C fibers result in the release of excitatory amino acid neurotransmitters (glutamate) and neuropeptides, particularly substance P. This in turn results in activation of WDR and nociceptive neurons. The receptors for the excitatory amino acid at the spinal level are the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), the kainate, the N-methyl-D-aspartate (NMDA) and the metabotropic ACPD receptors.⁷ AMPA receptors mediate the majority of fast excitatory transmission of glutamate. When released following acute painful stimuli, it will act on the AMPA receptor to produce short-lasting excitations. The NMDA receptor does not participate in "normal activity" pain circuit, and the activation of NMDA receptor is more complex. The receptor must bind to both glutamate and glycine and the membrane must be depolarized to allow the removal of the magnesium block. The latter process can be produced by the tachykinins co-released with glutamate following repeated C-fiber activity.⁸ Once the channel is open, a massive depolarization of the neuron results from the flux of calcium into the cell. The process also activates the calcium dependent protein kinase and triggers phosphorylation of the NMDA channels. As a result, the input signals to the dorsal horn will be amplified and prolonged, ie, the "wind-up" phenomenon. This sensitizes the wide, dynamic-range neurons in the dorsal horn, which allows A β touch input to trigger nociceptive transmission to higher centers. This may be the mechanism underlying various form of central hyperalgesia.⁹

Communication Between the Spinal Cord and Higher Centers

Nociceptive information is transmitted from the dorsal root ganglion to higher centers mainly through

the anterolateral quadrant of the spinal cord. In humans, the spinothalamic tract (SPT) is regarded as the most important pathway for nociceptive impulse transmission and mediate touch (cold and warm sensations as well as pain). It forms the basis for anterolateral cordotomy for intractable cancer pain. Most of the cells forming the SPT project to the contralateral thalamus. The SPT projecting to the lateral thalamus, such as ventroposterolateral nucleus, is involved in the sensory discriminative aspects of pain.⁴ The motivational-affective aspects of pain are probably transmitted by the SPT projections to the medial thalamus, as well as the spinoreticular and spinomesencephalic tracts. These pathways have been extensively reviewed elsewhere.¹⁰ Visceral pain is discussed later.

A major descending modulation pathway originates in the periaqueductal gray area, the locus ceruleus, and extends to the nucleus raphe magnus and the dorsal horn of the spinal cord via the dorsal longitudinal fasciculus before terminating in laminae I, II, and IV.

Opioid analgesics bind to opiate receptors in the descending pathway, thus mimicking the action of endogenous opioids. In humans, intracerebroventricular injection of opioids has been demonstrated in case series to provide powerful analgesia in patients suffering from pain secondary to head and neck cancers.^{11,12} Multiple opiate receptor types that produce pain relief independently have been described, indicating the complexity of these pain modulatory systems. Several theories proposed for the mechanism of opiate action include increased descending control, ascending modulation, direct brainstem inhibition, and direct cortical or thalamic inhibition.¹³ It is most likely that several of these mechanisms are simultaneously active and act synergistically within the central nervous system.¹⁴

Descending noradrenergic antinociceptive systems originating in the brainstem contribute to pain control, and α_2 -adrenergic receptors, predominantly the α_{2a} subtype, have been identified in the substantia gelatinosa of the dorsal horn. Both pre- and postsynaptic actions have been demonstrated.¹⁵ Stimulation of these α_2 receptors by intrathecal noradrenalin inhibits the firing of neurons stimulated by A δ and C fibers¹⁶ and the release of substance P in the dorsal horn.¹⁷ Recent evidence suggests that the antinociceptive effects of α_2 agonists may be due in part to acetylcholine release in the spinal cord.¹⁸ Intrathecal administration of clonidine had also been shown to abolish neuropathic pain in rats.¹⁹ When combined with an NMDA antagonist, these drugs exhibited a significant synergistic effect. In one multicenter randomized, controlled study,²⁰ clonidine administered via the epidural

route was shown to be effective in managing neuropathic pain in cancer patients.

Serotonin (5HT) is also recognized for its role in the descending control of pain. Central stimulation-induced analgesia is abolished when 5HT is depleted using p-chlorophenylalanine or the selective neurotoxin 5,6-dihydroxytryptamine. 5HT is thought to be an inhibitory transmitter in the dorsal horn. It is unclear which 5HT receptor subtype mediates its spinal antinociceptive effect.²¹

Somatic Cancer Pain

Somatic cancer pain can be caused by neoplastic invasion of bone, joint, muscle, or connective tissue. The local tumour mass produces and stimulates local production of inflammatory mediators, causing ongoing stimulation of peripheral nociceptors. Other sources of somatic cancer pain include bone fractures, reactive spasm of muscle overlying an area of tissue damage, postsurgical incisional pain, and radio/chemotherapy-induced pain syndromes. The most prevalent somatic pain syndromes are related to neoplastic bone involvement. Bone pain may be acute, chronic, or incidental in nature. It is typically dull, varies in intensity, causes local tenderness, and is exacerbated by weight-bearing or movement.

Mechanisms of Bone Pain

Direct tumour invasion of bone or the development of osseous metastases may account for persistent bone pain. Not all bone metastases are painful, and the pain is often disproportionate to the radiological findings. Nociceptive afferents are most concentrated in the periosteum, whereas bone marrow and cortex are less sensitive to pain. Some of the mechanisms contributing to neoplastic bone pain include stretching of the periosteum by tumour expansion, local microfractures that cause bony distortion, nerve compression due to either collapsed vertebrae or direct tumour encroachment, and local release of algesic substances from the bone marrow.²²⁻²⁴

Bone pain has been correlated with osteoclastic activity.²⁵ In normal bone, the net activity of bone resorbing cells (osteoclasts) equals the net activity of bone-forming cells (osteoblasts). In metastatic disease, there is evidence of increased osteoclastic activity. Both tumor and humoral factors, including prostaglandins, cytokines, local growth factors, and parathyroid hormone, enhance osteoclastic activity and act locally to stimulate nociceptors. Despite increased osteoclastic activity, bone formation also increases.^{26,27}

With this increased turnover of bone, the proportion of immature, undermineralized bone increases and thus the likelihood of fracture increases. The metabolic activity of bone is a predominantly surface-based phenomenon.²⁶ Since cancellous bone provides a large surface area compared with cortical bone, it is not surprising that neoplastic disorders of bone remodelling are expressed earlier at cancellous sites.

Clinical Implications

Opiate analgesics, which form the basis of cancer pain treatment, are used frequently for mild to moderate bone pain and can provide good baseline analgesia. For opioid-resistant bone pain, adjuvant analgesics and other treatment modalities should be considered. Non-steroidal anti-inflammatory agents (NSAIDs) are particularly useful for bone pain since many of the symptoms are related to local inflammation. NSAIDs act on cyclooxygenases to inhibit prostaglandin synthesis and reduce local edema and prostaglandin-induced sensitization. Bisphosphonate drugs are increasingly being recognized for use in bone pain management. They selectively inhibit osteoclastic bone resorption and may exert a possible anti-inflammatory effect.²⁸ This could account for some of their analgesic effect. Several double-blind, placebo-controlled phase III trials in breast cancer and multiple myeloma patients given monthly infusions of pamidronate, a bisphosphonate drug, showed improvement of bone pain and a reduction in skeletal complications such as fractures and spinal cord compression.²⁹

The treatment of choice for metastatic bone pain is radiation therapy. It is thought to act by reducing local inflammation and by tumor shrinkage.³⁰ The pain relief from radiation therapy can be very durable. In patients who survive for a year or more and are pain-free following radiation therapy, 60% will remain so.³¹ In certain situations, radioisotopes can be useful. Radioisotopes are unstable and decay to daughter elements, with the subsequent release of ionising radiation. Bone-specific isotopes such as strontium-89 are preferentially taken up at sites of osteoblastic activity and are incorporated into the mineral structure of bone. Strontium-89 emits β -radiation within the bone to a distance of 8 mm.³² Uptake is greatest in patients with widespread metastases who have a marked osteoblastic activity, as happens in bone metastases secondary to prostatic carcinoma.

Incidental or movement-related pain is difficult to control. If both pharmacological and radiation therapy fail to control incidental pain, anaesthetic techniques such as patient-controlled epidural analgesia (PCEA) may be of use. PCEA can provide continuous baseline

analgesia, with the facility for on-demand bolus doses prior to movement. A judicious combination of these therapeutic options can provide good symptom control in patients with bone pain. However, bone pain remains a significant problem for cancer patients and provides us with a clinical challenge.

Visceral Cancer Pain

Certain clinical characteristics are peculiar to visceral pain. Some viscera are apparently insensitive to pain. Solid organs such as lung, liver, and kidney parenchyma are insensitive, despite gross destruction by malignancy, and pain is signalled only when capsular or adjacent structure is involved. Harmful stimuli such as burning or cutting of visceral tissue do not cause pain, whereas natural stimuli such as hollow-organ distension readily produces pain. Visceral pain is often diffuse and poorly localized, and it is sometimes referred to other nonvisceral structures, making the source of the pain difficult to elucidate. Visceral pain may be accompanied by autonomic reflexes such as nausea. The physiological significance of these properties is not yet fully understood.³³

Mechanisms of Visceral Pain

Receptors — Recent research has shown that there are two distinct classes of nociceptive sensory receptors in viscera.³⁴ The first class is composed of “high-threshold” receptors that respond to mechanical stimuli within the noxious range. These have been identified within many viscera, including the heart, lungs, gastrointestinal tract, ureters, and urinary bladder.³⁵ The second class is composed of receptors that have a low threshold to natural stimuli and encode the stimulus intensity in the magnitude of their discharges, the so-called “intensity-encoding” receptors. Both receptor types are mainly concerned with mechanical stimuli such as stretch and are involved in the peripheral encoding of noxious stimuli in viscera.³⁶ Experimental data suggest that viscera contain nociceptive afferents that are normally considered “silent.”^{37,38} In the presence of local inflammation or tissue injury, these afferents become sensitized and respond to previously innocuous natural stimuli. The clinical significance of this inflammation-induced sensitivity is unknown. High-threshold afferents signal acute visceral pain. Local ischemia, hypoxia, and inflammation cause pain by sensitizing high-threshold receptors and these previously “silent” or unresponsive receptors. Inflammatory mediators released locally lower their firing threshold and, by peripheral sensitization, augment and perpetuate the transmission of noxious stimuli.³³

Triggering Factors — Pain in visceral structures is not necessarily linked to tissue injury, but rather is dependent on the nature of the provoking stimulus. An adequate stimulus refers to the stimulus that produces a given sensation.³⁹ Adequate stimuli that induce pain are distension, ischemia, and inflammation. Hollow organs such as the colon are very sensitive to luminal distension or inflammation but are totally insensitive to cutting or burning stimuli. Pain induced by colonic distension is dependent on the distending pressure rather than the volume.⁴⁰ It has been shown that the intraluminal pressure in the colon required to produce a painful sensation is 40 to 50 mm Hg. Hence, a tumor may continue to grow undetected if it fails to exert this intraluminal pressure and may cause pain only at a much later stage when there is complete obstruction of the lumen and a significant rise in intracolonic pressure. Solid organs are least sensitive, whereas the serosal membranes of hollow organs are most sensitive.⁴¹

Pathways — Viscerosensory information is relayed from the periphery by afferent fibers in sympathetic and parasympathetic nerves.³⁴ Nociceptive afferents from thoracic and abdominal viscera travel along the path of visceral sympathetic efferent fibers. Thoracic nociceptive afferents travel to the thoracic splanchnics before converging onto the paravertebral sympathetic trunks and then entering the dorsal horn. Abdominal nociceptive afferents travel to the celiac plexus and the thoracic splanchnics prior to entering the sympathetic trunks and dorsal horn. In contrast, the pelvic visceral nociceptive afferents converge on the pelvic splanchnic nerves, which are primarily parasympathetic efferent fibers. Some pelvic afferents also pass through the lumbar sympathetic splanchnic nerves. On entering the dorsal horn, visceral afferents terminate on spinal cord lamina I and V. Visceral afferents constitute 10% of all afferent inflow into the spinal cord.³⁴ This is a relatively small number when considering the large surface area of some organs. However, the number of dorsal horn neurons that respond to visceral stimulation is estimated to be 56% to 75%, suggesting functional divergence of these neurons. There are no neurons that respond exclusively to visceral afferents. Both anatomic and electrophysiologic studies have demonstrated viscerosomatic convergence in both the dorsal horn and supraspinal center.⁴² There is also evidence of viscerovisceral convergence onto these second-order neurons. Examples include the convergence of pelvic visceral inputs such as colon/rectum, bladder, uterine cervix, and vagina.^{39,43} Poorly localized visceral pain may be explained by the low density of visceral nociceptors, the functional divergence of visceral input with the central nervous system, and viscerovisceral convergence in the spinal cord.

In addition to the spinothalamic and spinoreticular tracts, three new pain pathways have been identified in the spinal cord — the dorsal column pathway, the spinoparabrachioamygdaloid pathway, and the spinohypothalamic pathway. The dorsal column pathway differs from the spinothalamic neurons in that it ascends ipsilaterally near the midline before terminating in the nucleus gracilis. From there, internal arcuate fibers transmit nociceptive input to the ventroposterolateral (VPL) nucleus of the thalamus. Recent work by Al-Chaer and colleagues^{44,45} has identified the dorsal column as being more important in visceral nociceptive transmission than the spinothalamic and spinoreticular tracts. In monkeys, colorectal distension stimulates firing of viscerosensitive (VPL) neurons. After a dorsal column lesion at T10 level, the responses were dramatically reduced despite ongoing stimulation. Interestingly, a similar lesion of the SPT at T10 does not achieve the same effect.⁴⁶ Further animal studies have recently reported that the dorsal column also has a role in signalling epigastric nociception.⁴⁷ These newly identified pathways have led to new clinical approaches in managing visceral cancer pain. In humans, midline myelotomy has been used to treat visceral pain. Its success is clearly not due to interruption of the decussating fibers of the SPT, as was previously thought.⁴⁸⁻⁵⁰ This procedure has been performed successfully for pelvic cancer pain and did not produce neurological sequelae.

Referred Pain — Visceral pain may be localized to distant and often superficial somatic structures such as muscle or skin. A common example of referred pain is the shoulder, abdominal, and back pain that occurs with pancreatic carcinoma. Viscerosomatic convergence provides a convincing explanation for “referred pain.” This “convergence-projection” theory proposes that the activity in ascending spinal pathways is misconstrued as originating in somatic structures because of previous experiences of somatic pain.³⁴ When somatic structures are invaded by visceral malignancies, further localized pain may ensue. Local hyperalgesia may occur at the referral site. This may be due to a combination of central sensitization as a result of continual noxious visceral input and peripheral algogenic mechanism.⁴²

Clinical Applications

Visceral pain can be managed by both pharmacological and interventional techniques. Combinations of opioids, NSAIDs, and adjuvant medications form the mainstay of therapy. When pharmacological therapies prove ineffective or are limited by side effects, regional anesthesia techniques or neurosurgical techniques should be considered. The former techniques involve the administration of local anesthetics, opioids, or neurolytic agents to the neural axis or visceral plexi. The

Possible Mechanisms of Neuropathic Pain

- Peripheral sensitization
- Ectopic foci of hyperexcitability in neuron
- Sympathetic maintained activity
- Loss of inhibition of dorsal horn neuron
- Central sensitization
- Rewiring of synaptic connection in the dorsal horn
- Phenotypic switch

goals of these interventional procedures are to provide superior analgesia and to allow for a decrease in opioid consumption.

Continuous epidural or intrathecal infusion of local anesthetics or opioids can be effective for controlling abdominal or pelvic cancer pain. In a retrospective review of 51 patients with terminal cancer who experienced inadequate pain relief after oral medication and/or manifested intolerable side effects, intrathecal infusion of opioids improved the pain control in 66% of the patients. By adding local anesthetic to the opioids, the analgesic effect was improved to 94% of the patients.⁵¹ Autonomic supply to the liver, pancreas, spleen, kidneys, intestines, and suprarenal glands arises in the celiac plexus. Hence, neurolytic block of celiac plexus is indicated for visceral pain from cancer in the upper abdomen, especially when pancreatic in origin.⁵² Pelvic pain due to tumor invasion can be successfully managed by neurolysis of the superior hypogastric plexus, while perineal pain due to pelvic cancer can be eased by blockade of the ganglion impar.⁵³ Ablative neurosurgical techniques are used less often than in the past, but for patients with refractory unilateral cancer pain, percutaneous cordotomy may still be useful. The recently described dorsal column pathway may also offer therapeutic options for the future.

Neuropathic Cancer Pain

Neuropathic pain results from damage or inflammation of the nervous system, either peripheral or central. Only peripheral neuropathic pain will be discussed here. In patients with cancer, peripheral neuropathic pain can be caused directly by infiltration or compression of the nerve by the tumor or indirectly by cancer treatments such as radiation therapy and chemotherapy (eg, vincristine). In debilitated patients, herpes zoster is common, and post-herpetic neuralgia may follow.

Neuropathic pain is characterized by the following pain symptoms: spontaneous burning pain with an intermittent sharp stabbing or lancinating character, an

increased pain response to noxious stimuli (hyperalgesia), and pain elicited by nonnoxious stimuli (allodynia). The relationship between mechanism and symptomatology is complex. The underlying mechanism can be different for the same symptom, while the same mechanism can result in different symptoms. Suggested mechanisms are summarized in the Table.

Mechanisms of Neuropathic Pain

Spontaneous firing of C-fiber nociceptors and low-threshold A β -fiber mechanoreceptors has been reported after nerve injury in humans.⁵⁴ Following nerve injury, sodium channels accumulate both at the site of injury and along the length of the axon.⁵⁵ These sodium channels form foci of hyperexcitability that result in ectopic action potential discharge in the axon and cell body of the nerve fiber. Sympathetic activity also plays a role in the mechanism of spontaneous pain. Expression of α -adrenoreceptor in injured and uninjured axons can occur after nerve injury, rendering them sensitive to circulating catecholamines. Nerve injury can induce growth of sympathetic axons around the sensory neurons in the dorsal root ganglion.⁵⁶ Dorsal horn neurons act as the "gate-keepers" for nociceptive transmission, receiving both excitatory input from sensory neurons and inhibitory input from the spinal cord and higher centers. Peripheral nerve injury may reduce inhibitory control over dorsal horn neurons through various mechanisms.⁵⁷ This may result in spontaneous firing of dorsal horn neurons or an exaggerated response to the noxious stimuli.

Central sensitization is an important mechanism of hyperalgesia and allodynia. The mechanism has been discussed in the previous section. The resultant effects will be expansion of the peripheral receptor field where a stimulus will activate neurons, increased response to a noxious stimulus, and initiation of action potential discharge from subthreshold input.⁹ There are two additional mechanisms for allodynia.

Peripheral nerve injury can induce sprouting of A β -fiber central terminal into lamina II, which normally receives only nociceptive information from C fibers. As a result, the low-threshold information from large A β afferents that is normally perceived as touch may now be misinterpreted by the nervous system as pain. Peripheral nerve injury can also result in expression of neuropeptides usually involved in nociception such as substance P and calcitonin-gene-related peptide in A β fiber, a phenomenon called phenotypic switch. Thus, A β fibers, upon stimulation by low-threshold stimuli, will release substance P in the dorsal horn and thereby generate a state of central hyperexcitability normally produced only by nociceptive input.

Clinical Implications

The effectiveness of opioids in the management of neuropathic pain is controversial.⁵⁸ In the spinal cord, the opioid receptors mu, delta, and kappa are found in presynaptic sites on the afferent nociceptive fiber terminal and postsynaptic sites located on the secondary neuron of nociceptive circuitry. The highest concentration of opioid receptors are around the C-fiber terminal zone in laminae I and II, and greater than 70% of mu receptors are on the afferent presynaptic terminals.⁵⁹ Peripheral nerve section will lead to loss of all the pre-synaptic opioid receptors. This is likely to result in a marked reduction of opioids receptors pool at the spinal level, and it contributes to the opioid insensitivity in neuropathic pain states.⁸ Another transmitter, cholecystokinin (CCK), also plays a major role in the control of opioid sensitivity at both the spinal and supraspinal level. The application of CCK can selectively reduce the analgesic actions of morphine, and antagonists of the CCK-B receptor enhance morphine analgesia. It has been found that CCK is upregulated after nerve damage or in neuropathic models.^{60,61}

Neuropathic pain normally responds poorly to systemic opioids.⁵⁸ Although the insensitivity can be relative, the greater dose of opioids can produce intolerable or unmanageable adverse effects that renders opioid therapy undesirable. In contrast, intrathecal administration of morphine was shown to produce greater dose-dependent inhibitions of neuronal responses to noxious and C-fiber-evoked stimuli compared with those by the systemic route in spinal nerve ligated rats.⁶² The problem of opioid responsiveness in neuropathic pain states may not simply be that of a reduced opioid sensitivity, but rather the failure to deliver a sufficiently high concentration of the systemic opioids to the spinal cord in the absence of adverse effect.⁶²

Sodium channel blockers (local anesthetic, antiarrhythmic, and antiepileptic drugs) are the mainstay treatments in neuropathic pain. There are two types of sodium channels — one sensitive and the other insensitive to tetrodotoxin, a potent puffer-fish toxin. The sodium channels that are sensitive to tetrodotoxin exist in all sensory neurons, while the channels that are insensitive to tetrodotoxin are found only on nociceptive sensory neurons and are implicated in pathological pain states.⁶³ After nerve injury, sensory afferents may display ectopic discharge properties due to accumulation of sodium channels in the injured and uninjured neurons, with the tetrodotoxin-insensitive sodium channels particularly implicated in the latter. Sodium channel blockers that are currently available are not selective enough; their clinical use will result

in undesirable central nervous system and cardiovascular system side effects.

Sympathetic activity has been implicated in the generation of neuropathic pain. Specific treatments such as sympathetic block, intravenous regional guanethidine block, or α_1 antagonists have been used widely in recent years. However, evidence to support their use is limited, and only a small proportion of patients benefit from these treatments.⁶⁴ Loss of inhibitory regulation in the dorsal horn contributes to spontaneous firing of nociceptive pathways through various mechanisms. Levels of gamma-aminobutyric acid (GABA, an inhibitory transmitter in the dorsal horn) are reduced, and GABA receptors on the dorsal horn neurons are downregulated. Gabapentin, an anticonvulsant that is structurally related to GABA but does not act on GABA receptors, has been shown to be efficacious for the treatment of neuropathic pain of various etiologies.^{65,66}

NMDA antagonists have been used in an attempt to abolish wind-up at the spinal cord level. Ketamine, a NMDA antagonist, has been shown to be a potent analgesic at subanesthetic doses.⁶⁷ It may reduce hypersensitivity in the dorsal horn. Both ketamine and amantadine have recently been shown to reduce opioid-resistant neuropathic pain in cancer patients.^{68,69} Therapeutic synergism is seen when ketamine is added to morphine. This can be explained by their differing actions on wind-up.

Conclusions

Advances in knowledge in neurophysiology, neuroanatomy, and pharmacology have allowed a greater understanding of the peripheral and central mechanisms of pain. Cancer pain can be defined on the basis of the structures involved, ie, somatic, visceral, and neuropathic cancer pain syndromes. Acute, chronic, or sometimes intractable pain may result. Clinicians should possess a working knowledge of the etiology and mechanisms of these syndromes before addressing difficult cancer pain problems. Newer, more sophisticated drugs and interventional techniques have advanced our levels of expertise in controlling cancer pain.

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