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Bioactive Substances and Receptors for Pain Modulation in the Spinal Cord

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Introduction

The transmission of pain from peripheral tissues through the spinal cord to the higher centers of the brain is not a passive simple process using exclusive pathways. Since the spinal neuronal systems have the potential to alter the information, the input messages may be attenuated or enhanced. Thus the interplay between spinal neuronal systems will determine the messages delivered to higher levels of the central nervous system.

In the early 1980s a study on central plasticity in the somatosensory system led to the discovery that tissue injury could trigger an increase in the excitability of neurons in the spinal cord, a phenomenon that has become known as central sensitization. It was then found that central sensitization was generated by C-afferent fibers and that the changes were expressed as alterations in the spatial extent, responsiveness and threshold of the receptive fields of dorsal horn neurons as a consequence of the recruitment of subthreshold synaptic potentials.

Facilitation in the dorsal horn occurs as a direct consequence of increased C-fiber input. This "Wind-up" phenomenon is due partly to the interaction of two mediators released from the C-fiber terminals, namely glutamate which acts on AMPA and NMDA receptors and substance P which acts on neurokinin (NK)-1 receptors. Other modulating influences, whose activity may be altered in

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**Fig. 1** Spinal cord synaptic plasticity. A schematic diagram illustrating the release of the excitatory and inhibitory transmitters and subsequent effects on a dorsal horn nociceptive neuron, wind-up and gene induction for example. Transmitters are derived from either the afferent C-fibers, interneuron, or descending bulbospinal pathways. Transmitters such as glutamate, substance P, neurokinin A, and CGRP contribute to excitatory modulation whereas 5-HT, NE, enkephalin, somatostatin, adenosine, GABA, and glycine contribute to inhibitory modulation.
chronic pain states, include GABA-mediated inhibition, and an alterations in opioid-mediated synaptic inhibition due partly to increased release of cholecystokinin (CCK) acting in opposition to endogenous opioids1. Many other peptide and non-peptide mediators are believed to modulate transmission in the nociceptive pathway. There are two types of modulation, excitatory and inhibitory as depicted in Fig 1. The excitatory modulation means enhancement of the intensity and/or duration of the nociception, and inhibitory modulation means alleviation of the nociception. Therefore, the excitatory or inhibitory modulation does not necessarily coincide with the direct action on the neuronal membrane activity. In this article, the new development of neuroscience concerning the mediators and receptors in the spinal cord is reviewed. The spinal receptor systems and bioactive substances are summarized in Table 1.

Table 1. Summary of spinal receptor systems and bioactive substances.

<table>
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<tr>
<th>Classification</th>
<th>Substance</th>
<th>Receptor</th>
<th>Spinal binding site</th>
<th>Spinal effects</th>
<th>Agonist</th>
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Location of binding in spinal cord; some transmitter bind presynaptically on primary afferent nerve terminals, others bind postsynaptically. The spinal effects of ligands are modulation of substance P release and the discharge of WDR neuron in the spinal dorsal horn. Abbreviations: SP; substance P; GABA; gamma-amino-butyric acid; WDR; wide dynamic range; NMDA; N-methyl-D-aspartate; AMPA; a-aminomethyl-5-hydroxy-5-methylisoxazole; NK; neurokinin; 5-HT; 5-hydroxytryptamine; DPDPE; D-Pen2-D-Pen5 enkephalin; NPY; neuropeptide Y.
Excitatory Modulation

Neuropeptides

Tachykinins

The tachykinins belong to a family of neuropeptides, including substance P (SP), neukokinin A (NK₆₆) and neukokinin B (NK₆₇). There are three major types of tachykinin receptors (NK-1, NK-2 and NK-3) which recognize these peptides⁶, SP being the preferred agonist at NK-1 receptors⁶. In the human CNS, NK-1 receptors predominate and are believed to play a major role in pain transmission.

Tachykinins, particularly SP, the most intensively studied sensory neuropeptide, are known to be important mediators in the nociceptive pathway⁴. SP is released, along with NK₆₆, in the spinal cord in vivo upon noxious peripheral stimulation. In acute nociception, NK₆₆, acting on NK-2 receptors, appears to play the major role. NK-1 antagonists have only a small effect on the slow excitatory synaptic potential in the spinal cord elicited by C-fiber stimulation, whereas NK-2 antagonists are much more effective, suggesting that, under normal physiological conditions, SP is less important than other excitatory transmitters (particularly NK₆₆), in this pathway⁴. Accordingly, NK-1 receptor antagonists produce only a weak inhibition of acute nociceptive responses.

NK-1 receptors are upregulated during hyperalgesic conditions and the production and release of tachykinins from primary afferent fibers also increase⁸. In the spinal cord the parallel increase in the amount of SP released and in the number of NK-1 receptors both contribute to the enhancement of SP-mediated transmission. SP produces long lasting depolarization of dorsal horn neurons. This contributes to the long lasting facilitation of transmission ("wind-up") in the nociceptive pathway that follows activity in peripheral nociceptive neurons.

NK-1 receptor antagonists are antinociceptive in various animal models in which hyperalgesia is allowed to develop. Peptide antagonists specific for NK-1 and NK-2 receptors have been known for several years, and used to study the functional role of these receptors, but have not been developed for therapeutic use.

Neurotensin

Neurotensin, a tridecapeptide first isolated from bovine hypothalamus⁶, produces a variety of pharmacological effects in vitro as in vivo. In the rat spinal cord, neurotensin has been localized to the substantia gelatinosa as a particularly dense band of fiber and terminal like fluorescence in lamina II, with somewhat lower density in lamina I⁸.

Neurotensin causes a slight to moderate excitation of nociceptor afferent fibers in laminae I-III. This excitation is characterized by a slow onset and recovery. The temporal characteristics of neurotensin-produced excitation and the results with L-glutamate are consistent with the possibility that neurotensin acts on postsynaptic sites in laminae I-III of the spinal cord as a neuromodulator⁸.

Calcitonin gene related peptide (CGRP)

CGRP is released from nociceptive afferent fibers in the dorsal horn in response to noxious stimuli. It produces slow depolarizing responses in dorsal horn neurons, and also potentiates the depolarizing effect of SP. The coexistence of CGRP and SP in neurons within the dorsal root ganglion and the spinal cord dorsal horn reveals that these two neuropeptides have functionally important interactions⁴. CGRP can potentiate the release of SP from spinal dorsal horn neurons⁶. Capsaicin, a compound which stimulates the release of SP, can produce the release of CGRP from rat spinal cord slices. One possible mechanism by which CGRP could potentiate SP evoked activity may be through excitation of spinal dorsal horn neurons which receive input from primary afferent neurons. CGRP has been demonstrated to produce a Ca²⁺ dependent depolarization in dorsal horn neurons⁶ and to excite wide dynamic range and low threshold mechanoreceptive neurons when applied iontophoretically⁶.

Cholecystokinin

CCK differs from most of the other neuropeptides that modulate nociceptive transmission in that it appears to act, not directly, but by interaction with the opioid system; it can be regarded as an endogenous inhibitor of opioid mediated analgesia⁵. CCK given intrathecally antagonizes the analgesic effect of opiates acting on the mu-receptors, but does not by itself produce hyperalgesia under normal conditions. Under conditions of stress, when the antinociceptive opioid systems are activated, CCK produces hyperalgesia, similar to that produced by naloxone. Conversely, CCK antagonists enhance the analgesic effect of opiates⁸. This accentuation is clearly evident in normal animals, but under conditions of chronic inflammation, in which the antinociceptive potency of morphine is enhanced compared with the normal situation, CCK antagonists have no effect. Many neuropathic pain states are associated with hyperalgesia and allodynia which are relatively resistant to opiates. It is suggested that this results from increased release of CCK, since CCK antagonists enhance the effect of morphine in animal models of neuropathic hyperalgesia⁸.
**Amino acids**

Glutamate

Many literatures support involvement of receptors for excitatory amino acids (EAA), especially glutamate, in mediating synaptic transmission in the mammalian spinal cord. The existence of at least 3 EAA receptor subtypes has been described including those activated by the agonists N-methyl-D-aspartate (NMDA), quisqualate (Quis) or the more selective agonist, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)\(^2\), and kinate (KA)\(^3\). The NMDA and AMPA receptors are involved in spinal nociceptive transmission. Especially NMDA receptors are located in the dorsal horn neurons in laminae I and V, areas of the spinal cord thought to receive nociceptive input. Both NMDA and AMPA at subthreshold doses can elicit increased responses to peripheral mechanical, especially noxious mechanical, and noxious thermal stimulation of dorsal horn projection neurons.

Antagonists at NMDA receptors, such as AP-5 and MK801, prevent the phenomenon of "wind-up" in the spinal cord\(^4\), which is believed to play an important role in inflammatory hyperalgesia\(^5\), and show analgesic activity in various animal models when administered intrathecally. Ketamine, is effective as an analgesic agent, given on its own or as an adjunct to morphine\(^6\). Another clinically available drug, the antiviral agent memantine, also possess NMDA blocking activity, and has been shown to be antinociceptive in the formalin test in rats, with a reasonable margin between this action and disturbance of motor function\(^7\).

**Inhibitory Modulation**

**Neuropeptides**

Opioids

It has become increasingly clear that the powerful analgesic effects of opiates result from actions at both spinal and supraspinal sites\(^8\). Modification of spinal nociceptive processing by systemically administered opiates results both from local actions within the dorsal horn and from supraspinal actions that activate descending antinociceptive systems. At spinal level, the intra-thecal administration of opiates or opioid peptides elicits behavioral analgesia in animals and in man.

Opioid receptors in the spinal cord are a key site in the production of analgesia, as demonstrated by opioid inhibition of nociceptive neurons in spinal animals, direct analgesia following epidural and intrathecal opioids in animals and then subsequently in humans\(^9\). There have been considerable efforts devoted to the study of opioid receptor subtypes in the spinal cord, using both electrophysiological and behavioral approaches.

There are three opioid receptors in spinal cord, mu, delta and kappa. Morphine acts on the mu receptor\(^\circ\). The highest concentrations of opioid receptors in the spinal cord are around the C-fiber terminal zones in the lamina I and the substantia gelatinosa with lower concentrations found in the deeper layers\(^9\).

The location of the presynaptic opioid receptors on C but not large A-fiber terminals allows for the observed selective effects of spinal opioids on noxious evoked activity\(^9\). Many of the postsynaptic opioid receptors are located on nociceptive circuitry such as interneurons or on the dendrites of the deep cells penetrating into the C-fiber terminal zone; inhibitory effects here would also be selective. Whatever the case these different mechanisms will have overall similar final effects in reducing acivity in nociceptive pathways.

Fleetwood-Walker et al.\(^10\) reported that when administered near to spinocervical tract (SCT) neurons in laminae III - V of cat spinal cord, only kappa agonists exerted a selective antinociceptive action whilst mu and delta agonists were ineffective. In contrast, mu agonists iontophoretically applied in the region of the substantia gelatinosa had a selective antinociceptive effect on SCT neurons.

The antinociceptive action of kappa opioid agonists is exerted on both the thermal and mechanical nociceptive responses of laminae III - V neurons to an apparently similar degree. Systemic or intrathecal administration of selective kappa agonists are most effective against visceral and mechanical nociception but there is little margin between doses causing antinociception and motor dysfunction or paralysis\(^10\).

Mu and delta receptor selective agonists often had profound influences on both nocispecific and multisensory lamina I neurons. Autoradiographic studies have revealed mu opioid binding sites correspondingly concentrated in the superficial dorsal horn (lamina I and III)\(^9\) and mu agonists can exert an antinociceptive influence on deeper dorsal horn neurons, via the substantia gelatinosa, in cat.

A recent autoradiographic study by Morris and Herz\(^10\) found delta binding sites restricted to lamina I of the dorsal horn of the rat. So delta agonists failed to influence somatosensory inputs to deeper dorsal horn neurons (lamina III - V) when either applied nearby these cells or in the substantia gelatinosa dorsal to the cells being recorded.

In 1979, Wang et al.\(^11\) reported the first use of spinal intrathecal opioid in humans, who were eight patients with intractable pain due to malignancies of the genitourinary tract with invasion of the lumbosacral plexus. The use of intrathecal opioids for acute and chronic pain relief subsequently was reported in many clinical settings,
Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is a 36-amino acid peptide derived by the posttranslational processing of a 97 amino acid precursor molecule. In the spinal cord, a rich system of NPY like immunoreactivity, particularly in the superficial layers of the dorsal horn and in the intermediolateral cell column has been described. The origin of endogenous NPY in the dorsal horn as well as in other parts of the normal spinal cord is considered to be primarily from intrinsic interneurons and from descending bulbo spinal projections. NPY is shown to be a powerful modulator of neurotransmitter release from cultured dorsal root ganglion cells and to yield a strong inhibition of spinal nociceptive and visceromotor reflexes following intrathecal administration in unanesthetized rats. Intrathecal administration of this peptide produces a powerful, dose-dependent blockade of noxious, thermal and mechanical stimuli which are not antagonized by an opioid or alpha 2 adrenergic receptor antagonists. Moreover, NPY strongly inhibits depolarization evoked release of substance P from cultured dorsal root ganglion neurons. The antinociceptive effects of NPY could possibly be mediated via the presynaptic inhibition of the release of substance P and other coexisting transmitters from primary afferent terminals. However, like for opiates, there is little in vivo evidence for the involvement of intrinsic NPY in the direct regulation of substance P content and release from the primary afferent fibers.

Somatostatin (SST)

SST is a tetradecapeptide extensively distributed in most organs of vertebrates. The somatostatinergic system includes afferent axons terminating in dorsal horn, spinal interneurons, and descending and ascending pathways. The use of spinal SST for pain control is extensive. Chrubasik et al. and Meynadier et al. reported that SST have analgesic actions for postoperative and cancer pain. But spinal SST in concentrations not much greater than those used in humans were found to have deleterious effects on the spinal cord after bolus intrathecal injections in rats, mice, and cats. SST or its analogues serve to decrease blood flow and to augment post synaptic effects of glutamate on spinal cord, then local neuronal injury might occur. In the light of these mechanisms, toxicological evaluation is needed for clinical use as analgesics.

Galanin

Galanin is another neuropeptide released by nociceptive afferent neurons. Unlike SP and CGRP, the synthesis of galanin is upregulated by peripheral nerve damage, and it is postulated that it exerts a tonic inhibitory effect on transmission in the dorsal horn. Galanin like agonists would therefore be a possible strategy for developing new analgesic drugs.

Amino acids

Gamma-aminobutyric acid (GABA)

GABA receptors and benzodiazepine receptors are localized in lamina II of the dorsal horn and moderately distributed in laminae I and III. High concentrations of GABA, GABA receptors and benzodiazepine receptors in lamina II of the dorsal horn of the human spinal cord suggest a possible role for GABA in spinal sensory functions. GABA receptors are evenly distributed throughout the gray matter of the spinal cord, although there are slightly more in the dorsal horn than in the ventral regions. The distribution of GABA receptors is not uniform. GABA receptors are located throughout the gray matter mainly in laminae II and III, but a considerable number of the
receptors also exists in laminae I and V and dorsal aspects of lamina X around the central canal.

The dorsal root potential is simulated by a GABA_A agonist, mucimol, and blocked by a GABA_A antagonist, bicuculline; the GABA_A receptors are on primary afferent nerve terminals. On the other hand, activation of GABA_A receptors inhibits the slow ventral root potential evoked by electrical stimulation. The location of the GABA_A receptors responsible for slow ventral root potential inhibition is not definite; possible sites include the receptors on the primary afferent nerve terminals, receptors on interneurons, and on the motor neurons themselves. Recently, baclofen has been shown to be a selective ligand for a bicuculline-insensitive GABA receptor (GABA_S) site. GABA_S receptors can occur presynaptically although a postsynaptic location is possible. The activation of GABA_S receptors reduces the evoked release of neurotransmitter. Such an action on terminals in the dorsal horn might well explain how baclofen acts an analgesic.

Some of the pharmacologic properties of barbiturates are due to actions on GABA receptors. Barbiturates enhance inhibitory synaptic transmission by increasing the effectiveness of the neurotransmitter GABA on the GABA_A receptor chloride channel. Propofol also occupies a site on the GABA_A receptor, which may be different from the sites occupied by the barbiturates or the benzodiazepines. Unlike clinically effective analgesic agents such as morphine and α_2-adrenoceptor agonists, propofol and barbiturates are not effective in suppressing nociceptive neurotransmission until they reach concentrations close to a general anesthetic level.

**Glycine**

Glycine and GABA are inhibitory neurotransmitters which appear to be important in sensory processing in the spinal dorsal horn. GABA is present in high concentration in the somata and axon terminals within laminae II and V. Glycine appears to coexist with GABA but not all GABAergic cells in the dorsal horn. Glycinergic neurons in laminae II and III of the rat spinal cord receive a major monosynaptic input from myelinated low threshold mechanoreceptive primary afferents which activate local glycinergic neurons in the dorsal horn. Glycinergic interneurons normally regulate the discharge of second order wide dynamic range neurons, the loss of this inhibitory regulation results in abnormal firing evoked by large diameter fibers.

Evidence of glycinerergic dysfunction in allodynia is provided by studies using the glycine receptor antagonist, strychnine.

**Others**

Norepinephrine

Alpha adrenoceptors on their synaptic locations led to a subdivision of α adrenergic receptors into postsynaptic α_1 and presynaptic α_1. As more selective α adrenoceptor antagonists became available, it was possible to definitely separate the α adrenergic receptors into two subtypes on a pharmacologic basis. The classification of α_1 versus α_2 is based on the antagonists yohimbine and prazosin.

The α_2 adrenergic receptors is a member of the G protein coupled family of membrane receptors. There are at least five separate effector mechanisms that are directly modulated by the activated α_2 adrenergic receptors. α_2 Adrenergic receptors activation results in the alkalization of the interior of cultured cells by accelerating Na⁺/H⁺ exchange. There also results activation of K⁺ channels and inhibition of voltage sensitive Ca²⁺ channels. α_2 Adrenergic receptors mediated inhibition of Ca²⁺ channels may play a role in suppressing Ca²⁺ entry into the nerve terminals and blocking exocytosis of neurotransmitters. Inhibition of calcium uptake has also been linked to the antinociceptive action of clonidine in rats.

Analgesic effects of α_2 adrenergic receptor agonists relate to the role of the descending medullospinal noradrenergic pathway modulating spinal nociceptive processing. α_2 Adrenergic receptors are located on the dorsal horn neurons of the spinal cord where they can either inhibit the release of nociceptive neurotransmitters such as SP or CGRP.

The analgesic action of clonidine, an α_2 adrenoceptor agonist, has been known for many years, and it is sometimes used by systemic or intrathecal administration for this purpose, usually in combination with other agents. The main disadvantages are sedation and hypotension. Used topically, as a transdermal patch, clonidine has also been reported to relieve hyperalgesia in patients with sympathetically mediated pain.

Dexmedetomidine, an α_2 receptor agonist used in veterinary anesthesia, is more potent in antinociceptive assays than clonidine when given intrathecally, but produces motor disturbances.

**Dopamine**

Several studies have indicated the presence of nerve terminals that contain dopamine in the dorsal horn of the spinal cord of the rat and cat. The use of compounds highly selective for D1 and D2 dopaminergic receptor subtypes provides direct evidence that iontophoretically applied dopamine exerts its antinociceptive effects via D2 dopaminergic receptors at the level of the dorsal horn. The precise location of dopaminergic receptors in the spinal cord is not clear but most likely location of these...
dopamine receptors may be interneurons. In the view of the action of dopamine on neurons in both laminae I and III-V, such interneurons may be located throughout the dorsal horn. Behavioral studies reveal that the selective antinociceptive effects of dopamine are mediated via D2 dopamine receptors. Barasi and Duggal reported that intrathecal administration of D2 dopamine receptor agonist, LY171555, significantly increased the tail flick latency of lightly anesthetized rats, while a D1 dopamine receptor agonist, SKF38393, had no effect. The selective inhibition of dopamine of nociceptive inputs to neurons with long ascending axons in both the superficial and the deeper dorsal horn indicates that the dopaminergic system can regulate both spinal nociceptive processing and the transfer of information to supraspinal levels.

Serotonin (5-HT)

Serotonin (5-HT) play an important role in modulating nociception. The spinal cord appears to be a major site for serotonin action, and intrathecally applied 5-HT produces dose dependent behavioral analgesia in rat, which can be reversed by 5-HT antagonists. The serotonergic innervation of the spinal cord originates from specific brainstem loci. In the dorsal horn, serotonergic terminals are concentrated in the superficial laminae I and II and the lateral aspects of laminae V and VI in the rat and cat. Electrical stimulation of nucleus raphe magnus, a major source of descending serotonergic input to the dorsal horn, can inhibit responses of dorsal horn neurons to noxious and innocuous stimuli. But inhibitory or excitatory effect of 5-HT are mediated through different classes of 5-HT receptor sites. In the spinal cord of rat, both 5-HT1A and 5-HT1B receptor subtypes are present. Although the 5-HT2 site also exists in the spinal cord, it is present at quite low levels.

Hamon et al. used radioactive ligands for 5-HT3 receptors, [3H] zacopride, the tritiated derivative of a highly potent and selective 5-HT3 antagonist, which was found in the superficial layers of the dorsal horn. 5-HT3 receptors are located presynaptically on unmyelinated primary afferent fibers within the spinal cord. Electrophysiological investigations have shown that 5-HT can exert both an inhibitory and an excitatory effect via different receptors probably, on primary afferent fibers. In addition, behavioral studies have revealed that analgesia can be obtained by either stimulation of 5-HT1 receptors or blockade of 5-HT3 receptors.

Adenosine

There is considerable evidence suggesting that adenosine exerts a modulatory effect on nociceptive transmission both in the periphery and in the central nervous system. Adenosine receptors fall into two main classes, A1 and A2. A1 receptors mediate predominantly inhibitory effects on synaptic transmission, whereas A2 receptors are mainly excitatory. Both receptor types are expressed in the central nervous system, and both types occur in the superficial region of the dorsal horn, where they are believed to be present on small interneurons. Intrathecal administration of adenosine analogues produces a powerful antinociceptive effect, though this is often accompanied by motor impairment. Systemic administration of adenosine agonists is also effective, but is accompanied by cardiovascular effects (hypotension and cardiac depression). Studies with receptor-selective agonists suggest that the antinociceptive action results from activation of A1 receptors, which is known to exert pre-and post-synaptic inhibitory effects in the dorsal horn. Adenosine receptor antagonists inhibit the antinociceptive action results from activation of A1 receptors. Adenosine receptor antagonists inhibit the antinociceptive effects of morphine, and morphine has been shown to elicit adenosine release. A1 receptor agonists act synergistically with opiates when both drugs are given intrathecally.

Acetylcholine

Histochemical and autoradiographic studies have demonstrated the existence of cholinergic nerve terminals and both muscarinic and nicotinic cholinergic binding sites in the spinal dorsal horn. Muscarinic receptors in the dorsal horn are located in the nerve terminals of the primary afferent. Muscarinic agonists may both excite and inhibit different dorsal horn cell systems raises the possibility that the antinociceptive actions of spinal muscarinic agonists reflect at least two modulatory mechanisms, one that excites inhibitory interneurons and one that hyperpolarizes dorsal horn projection neurons.

Both M1 and M2 muscarinic receptor subtypes are located in the superficial dorsal horn. The study in sheep is consistent with a predominant or exclusive role of M1 receptor subtypes in spinal cholinergic analgesia in this species. The spinal hemodynamic effects of intrathecally administered neostigmine in sheep are due to actions on M2 muscarinic receptors in the intermediolateral cell column, suggesting that cholinergically mediated analgesia and hemodynamic effects could be separated in this species with receptor selective agonists.

Phase I safety assessment of intrathecal neostigmine methylsulfate in healthy volunteers demonstrated dose related analgesia and side effects. Side effects observed were nausea, vomiting, urinary retention, motor weakness and decreased deep tendon reflexes. In contrast to systemic administration, relatively large doses of spinally administered cholinergic agonists or cholinesterase inhibitors increased blood pressure and heart rate. Volunteers
receiving spinal neurotensin in the current study exhibited
motor weakness and reduction in deep tendon reflexes in
the lower extremities, and later onset of the effects over
time was consistent with cephalic spread of neurotensin in
CSF.
Combining cholinergic agonists with either opioids or
adrenergic agonists may produce profound analgesia while
minimizing side effects.

Conclusions

Our knowledge about receptors operating in the spinal
cord in different pain situations has been increased re-
markably in the past few years. The concepts of central
hypersensitivity and plasticity are now the new range of
vision for development in neuroscience and pain medicine.
We now have a much better understanding of the events
underlying neuropathic and inflammatory pain. Antag-
nists of the neuropeptide and NMDA receptors, delta opioid
agonists, α2 adrenoceptor agonists, and CCK receptor
antagonists as analgesics would be used in the future.
However, we should further investigate and understand
the spinal receptors and neuropeptides and excitatory amino
acids which participate in pain modulation.

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54)요약된 제목: "요약은 인터넷에서 얻어진 최신 연구결과를 포함하며, 이를 통해 신경계의 기능을 이해하고 개선할 수 있는 발전을 도모하는 데 도움이 될 것입니다."
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