Pain is a complex sensation that has sensory-discriminative, cognitive-evaluative, and affective-emotional dimensions. Several areas distributed throughout the neuraxis exert a top-down modulation of pain sensation according to the nature of the painful stimulus and the behavioral state of the individual, both in normal and pathologic conditions. This modulation is largely mediated by descending monoaminergic pathways that either inhibit or facilitate transmission of nociceptive information at the level of the dorsal horn. Monoamines, including serotonin, norepinephrine, and dopamine, act via different receptor subtypes to exert a complex modulation of neurotransmitter release from nociceptive afferents and excitability of dorsal horn neurons. These monoaminergic systems have an important role in mechanisms of inflammatory and neuropathic pain and are a target for pharmacologic management of these conditions. A large number of experimental studies and the recent development of knockout mice models provide insights into the complex role of monoamines in the normal and abnormal pain processing in the spinal cord. This information helps to elucidate the pathophysiology of different pain disorders and the mechanism of action of drugs used for their treatment. Although histamine-mediated pathways may also contribute to descending modulation of pain transmission in the dorsal horn, this brief review focuses on the serotoninergic, noradrenergic, and dopaminergic systems, given their potential clinical implications.

**PAIN MODULATION NETWORK** The pain system encompasses the small diameter nociceptive afferents from dorsal root ganglion neurons; relay neurons of the dorsal horn projecting via the spinothalamic and spinobulbar pathways; local circuit dorsal horn neurons; and a distributed supraspinal network that modulates relay and processing of nociceptive inputs in the dorsal horn. Primary nociceptive afferents provide excitatory glutamatergic inputs to several laminae of the spinal dorsal horn, including lamina I (superficial dorsal horn), lamina II (substantia gelatinosa), and lamina V (deep dorsal horn). Some nociceptive afferents also release neuropeptides, such as substance P, which has an important role in mechanisms of sensitization of dorsal horn neurons in conditions such as neuropathic pain. Lamina I and lamina V project via the spinothalamic tract to the thalamus and via spinobulbar pathways to subcortical structures, including the parabrachial nucleus (which conveys these inputs to the hypothalamus and amygdala), periaqueductal gray (PAG), and rostral ventromedial medulla (RVMM). Lamina II contains inhibitory interneurons that utilize γ-aminobutyric acid (GABA), glycine, or opioids such as enkephalins, and provide both feedforward and feedback inhibition to the spinothalamic and spinobulbar projection neurons.

There are several areas of the CNS that, directly or indirectly, are activated by nociceptive inputs, targets of opioids, and participate in the central modulation of pain (figure 1). They include the prefrontal, anterior cingulate, and insular cortices; amygdala; periventricular and posterolateral hypothalamus; PAG; dorsolateral pons; and RVMM. These brain areas exert bidirectional influences on pain sensation as they may either inhibit or facilitate transmission of nociceptive inputs at the level of the dorsal horn. These modulatory effects are largely mediated by descending monoaminergic pathways that utilize serotonin, norepinephrine, or dopamine.

The effects of descending monoaminergic systems on nociceptive processing in the dorsal horn are com-
Monoamines may act via different subtypes of receptors located at the primary nociceptive afferents, dorsal horn projection neurons, local excitatory or inhibitory interneurons, and glial cells⁵,⁶,⁹ (table 1). Serotonin, norepinephrine, and dopamine may exert either antinociceptive or pronociceptive effects according to the type of receptor involved, site of action in the dorsal horn, and crosstalk between descending and local neurochemical signals, including adenosine, endogenous opioids, and nitric oxide⁵,⁶ (table 2). In addition, presynaptic reuptake via selective transporters and control of release via presynaptic inhibitory autoreceptors regulate the local concentration of monoamines and thus their effects on the targets in the dorsal horn.⁵

### Monoaminergic Modulation of Pain Transmission in the Dorsal Horn: Serotonin

Serotonergic inputs to the dorsal horn originate in neurons of the RVMM, including the nucleus raphe magnus and the nucleus reticularis magnocellularis. These neurons project to the superficial, and to a lesser extent deep dorsal horn. The RVMM receives a strong projection from the PAG; this PAG-RVMM serotonergic pathway has been classically considered the primary endogenous pain modulatory system and target of supraspinal opioid analgesia.⁷ However, the RVMM contains functionally heterogeneous groups of serotonergic and nonserotonergic neurons that are not only involved in pain modulation but also in control of autonomic and other homeostatic functions.¹¹ The RVMM contains two types of cells: OFF cells that are inhibited by noxious stimulation and excited by opioids, and ON cells that have an opposite pattern of response. The OFF cells have a net inhibitory effect on ascending nociceptive transmission, whereas ON cells facilitate nociception through activation of a descending pathway to the spinal cord.²¹¹

Serotonin, acting via different receptor subtypes, exerts complex modulatory effects on nociceptive transmission in the dorsal horn. Activation of 5-HT₁ receptors exerts an antinociceptive effect; postsynaptic 5-HT₁₅A receptors inhibit excitability of spinohalamic neurons and excitatory interneurons, whereas presynaptic 5-HT₁₃D receptors inhibit neurotransmitter release from primary afferents. The descending serotonergic pathways also have pronociceptive effects that appear to be mediated by 5-HT₂ and particularly 5-HT₃ receptors.³¹² The 5-HT₃ receptors are cation channels that elicit depolarization; presynaptic 5-HT₃ receptors increase neurotransmitter release from primary nociceptive afferents, whereas postsynaptic 5-HT₃ receptors increase excitability of STT neurons.

Studies on Lmx gene knockout mice, which lack brainstem serotonergic neurons, provide insights...
into the involvement of central serotonergic system in pain and analgesia. These mutant mice are less sensitive to noxious mechanical stimuli but exhibit more inflammatory pain compared to control mice. This indicates that central serotonergic neurons have a dual role in pain processing: they facilitate nociceptive transmission in response to mechanical stimuli but suppress the initial response to chemical activation of primary afferents and neurogenic inflammation.

**Norepinephrine.** The noradrenergic innervation of the dorsal horn originates from several cell groups in the pontine tegmentum, including the A5, A6 (locus ceruleus), and A7 groups. Whereas noradrenergic axon terminals innervate the cell bodies of both projection neurons and interneurons, volume transmission appears to be an important mechanism for noradrenergic modulation of neurotransmitter release from primary afferents. Norepinephrine primarily inhibits nociceptive transmission in the dorsal horn via presynaptic \( \alpha_2 \) (particularly \( \alpha_2 \lambda \)) receptors in primary nociceptive terminals. These receptors may also mediate postsynaptic inhibition of spinthalamic neurons. The algogenic effects of \( \alpha_2 \) receptor agonists, such as clonidine, also involve complex interactions with other antinociceptive neurotransmitter systems, including opioids and adenosine in the dorsal horn. Activation of postsynaptic \( \alpha_1 \) receptors may contribute to antinociception that increases release of GABA or glycine by local inhibitory neurons.

**Dopamine.** The main source of descending dopaminergic innervation of the dorsal horn is the A11 neurons of the periventricular posterior hypothalamus. Primary afferents and dorsal horn neurons in lamina I express both \( D_1 \) (\( D_1 \) and \( D_5 \))- and \( D_2 \) (\( D_2 \) and \( D_3 \))-type receptors. Although \( D_1 \) receptors are expressed at much higher concentration than \( D_2 \) or \( D_3 \) receptors, the \( D_2/D_3 \) receptors have higher affinities and are activated by lower concentrations of dopamine than \( D_1 \) receptors. Both acute and sustained noxious stimuli increase dopamine turnover in the dorsal horn, suggesting an enhancement of the activity of the descending dopaminergic pathway. Activation of A11 neurons reduces the behavioral responses to noxious stimulation, and this effect is mediated by \( D_2 \)-type receptors. These receptors elicit presynaptic inhibition of neurotransmitter release from primary nociceptive afferents. \( D_2 \) agonists may also elicit antinociception by potentiating the effects of endogenous opioids. In contrast, \( D_1 \) receptor stimulation elicits pronociceptive effects both directly and by antagonizing the actions of \( D_2 \) agonists or opioids. The effects of dopamine on spinal nociception may depend on its local concentration, as low levels may activate the antinociceptive \( D_2 \) type receptors, whereas high levels activate the pro-nociceptive \( D_1 \) receptors.

**Spinal monoamines and descending pain modulation.** Many brain areas involved in control of motivation, anxiety, fear, and mood strongly influence pain sensation. The prefrontal, anterior cingulate, and insular cortices, amygdala, and hypothalamus, project to the brainstem pain modulatory network, including the PAG, RVMM, and pontine noradrenergic cell groups. In addition, inputs from nociceptive dorsal horn neurons to the PAG, RVMM, and catecholaminergic cell groups provide for excitatory or inhibitory spino-bulbo-spinal feedback loops that are affected by these forebrain influences and may amplify the pain state. The overall balance between inhibitory and excitatory supraspinal signals mediated by monoamines provides the basis for top-down modulation of pain sensation according to motivation, emotion, and other behavioral variables and has an important role in mechanisms of inflammatory and neuropathic pain.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Source</th>
<th>Antinociceptive receptors (target)</th>
<th>Pronociceptive receptors (target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Locus ceruleus-subceruleus</td>
<td>( \alpha_2 ) (presynaptic)</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>A5 region</td>
<td>( \alpha_1 ) (inhibitory interneurons)</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>RVMM (NRM)</td>
<td>5-HT(_{1A}) (presynaptic and STT neuron)</td>
<td>5-HT(_3) (presynaptic and STT neuron)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>A11</td>
<td>( D_2, D_3 ) (presynaptic, possible STT neuron)</td>
<td>( D_1 ) (STT neuron)</td>
</tr>
</tbody>
</table>

RVMM = rostral ventromedial medulla; NRM = nucleus raphe magnus; STT = spinothalamic tract.

**CLINICAL CORRELATIONS** Neuropathic pain. There is experimental evidence that there is upregulation of central pain inhibitory control in cases of inflammatory pain, as a possible compensatory mechanism for central sensitization that occurs in this setting. In contrast, descending pain facilitation may promote a chronic pain state following nerve or spinal cord injury. This pronociceptive modulation may involve an excitatory spino-bulbo-spinal loop initiated from projections from the superficial
In the dorsal horn, serotonin, norepinephrine, and dopamine exert an antinociceptive action primarily by reducing neurotransmitter release from primary afferents; these effects are mediated by presynaptic 5-HT$_{1B}$, $\alpha_2$, and D$_2$/D$_3$ receptors, respectively. These receptors also contribute to postsynaptic inhibition of spinothalamic tract neurons. In contrast, serotonin acting via postsynaptic 5-HT$_3$ and both pre- and postsynaptic 5-HT$_3$ receptors, and dopamine, acting via D$_1$ receptors, may have a pronociceptive effect. Interneurons may also mediate the modulatory effects of monoamines. For example, norepinephrine may elicit antinociception via excitatory $\alpha_1$ receptors in local $\gamma$-aminobutyric acid (GABA)ergic neurons. Presynaptic reuptake and control of release by presynaptic inhibitory autoreceptors determine the local levels of monoamines and thus their effects on their different targets in the dorsal horn. DAT = dopamine transporter; NET = norepinephrine transporter; SERT = serotonin transporter.

Mechanism of action of analgesic drugs. Antidepressant drugs that block reuptake of monoamines, ligands of the $\alpha_2/\delta$ subunit of presynaptic voltage-gated calcium channels, and opioids constitute the mainstay of treatment of neuropathic pain. The analgesic effect of antidepressant has been classically attributed primarily to inhibition of reuptake of norepinephrine rather than serotonin, since the efficacy of selective serotonin reuptake inhibitors (SSRIs) is lower than that of serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine. However, studies in Lmx knockdout mice indicate that the involvement of serotonin in the mechanism of action of antidepressant drugs varies with the type of pain. The analgesic effect of both SSRIs and SNRIs during an acute thermal pain test was greatly reduced or absent in these animals lacking brainstem serotonergic neurons, suggesting that blockade of serotonin reuptake is the primary mechanism of the acute analgesic effects of antidepressants. In contrast, the analgesic effect of duloxetine in models of persistent pain was not affected by the loss of serotonergic neurons, indicating a critical role of norepinephrine for antidepressant-induced analgesia in chronic pain states.

Gabapentin and pregabalin are ligands of the $\alpha_2/\delta$ subunit of presynaptic voltage-gated calcium channels that inhibit neurotransmitter release from primary afferents. These drugs may also interact with the monoaminergic systems at both spinal and supraspinal levels. In rats with experimentally induced neuropathic pain, the inhibitory effect of gabapentin
on superficial dorsal horn neurons depends on its antagonistic interaction with hyperactive 5-HT₃ receptors. Gabapentin and pregabalin may also trigger a descending noradrenergic pathway that elicits analgesia via spinal α2 receptors.

Restless legs syndrome. There is evidence that restless legs syndrome (RLS) may reflect impaired function of descending dopaminergic pathways from the A11 cell group to the dorsal horn. Dopaminergic agonists that act via D₂/D₃ receptors are highly efficacious for treatment of this disorder. Animals with neurotoxic lesions of A11 neurons, or D3 receptor knockouts, provide experimental models of RLS. Patients with idiopathic RLS have static mechanical hyperalgesia to pinprick stimuli, suggesting central sensitization of small fiber input at the level of the spinal cord. This may reflect disturbance of dopaminergic pain modulation, as long-term treatment with D₂ receptor agonists reduces hyperalgesia in these patients. It has been suggested that augmentation (the worsening of symptoms following levodopa treatment) may reflect the relative shift from net D₂/D₃ receptor-mediated inhibition elicited by low spinal dopamine levels to D₁ receptor-mediated excitation elicited by high dopamine levels. Iron deficiency may predispose to augmentation by impairing the function of the dopamine transporter.

PERSPECTIVE The descending monoaminergic systems are the effectors of a distributed brain network that exert a top-down, bidirectional modulation of pain sensation according not only to the type of nociceptive input but also to attention, motivation, emotion, and other behavioral states. Experimental evidence indicates that monoaminergic modulation of spinal nociceptive processing is complex and varies with the type of pain. Recent studies in knockout mice provided further understanding on the differential role of specific monoamines in the pathophysiology of acute and chronic pain disorders and the mechanism of action of analgesic drugs. This information has clear therapeutic implications.

REFERENCES