Neurotransmitters Involved in Pain Modulation

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Introduction

Neurotransmitters that mediate fast synaptic transmission, like glutamate, gamma amino butyric acid (GABA), and glycine, cause rapid changes in membrane potential by opening ligand-gated ion channels (ionotropic receptors) present at discrete postsynaptic sites on target neurons. Other types of neurotransmitters modulate neuronal function in the dorsal horn but do not mediate fast synaptic transmission. Rather than activating ionotropic receptors at the synapse, these neurotransmitters generally act on metabotropic receptors outside the synapse. They function primarily via "volume transmission", whereby neurotransmitter molecules are released from nerve terminals into the extracellular fluid and then migrate to extrasynaptic receptors on the surface of the target cell to modify its function. These extrasynaptic receptors are often G protein-coupled receptors, which modulate neuronal activity via slower intracellular signaling pathways.

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Neurotransmitters Mediating Fast Synaptic Transmission in the Dorsal Horn

Glutamate is the main excitatory neurotransmitter mediating fast synaptic transmission in the dorsal horn. It is released from central terminals of primary nociceptors and promotes ascending transfer of nociceptive information by depolarizing and activating second order nociceptors (projection neurons) and excitatory interneurons. Glutamate receptors include AMPA, kainite, and NMDA receptors. Glutamate released from primary nociceptors also activates inhibitory interneurons, providing a modulating influence on pain transmission. Glutamate is also the neurotransmitter used by excitatory interneurons in the dorsal horn [1–3].

GABA and glycine are the main inhibitory neurotransmitters mediating fast synaptic transmission in the dorsal horn. They are released by inhibitory interneurons in the dorsal horn, which make synapses with primary nociceptor central terminals and projection neurons. GABA and glycine bind to their respective receptors, the $GABA_A$ receptor and GlyR, both of which are ligand-gated ion channels that are permeable to chloride ions. Although opening of these chloride channels usually causes hyperpolarization of the postsynaptic neuron, it can cause depolarization depending on the intracellular chloride concentration of the postsynaptic neuron. This occurs normally in primary nociceptor terminals, a phe-

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nomenon known as primary afferent depolarization (PAD). Despite the terminals being slightly depolarized, PAD still causes inhibition of synaptic transmission by inactivation of voltage-gated sodium and calcium channels, and by shunting [1–3].

Other Excitatory Neurotransmitters in the Dorsal Horn

Substance P is a neuropeptide present in dense core vesicles in the central terminals of peptidergic primary nociceptors. It can be released along with glutamate when these neurons are activated, especially during high intensity stimulation. The Substance P receptor, NK1, is a G protein-coupled receptor expressed by most projection neurons in lamina I. It is distributed across the entire cell membrane rather than being localized at synapses, and Substance P can thus diffuse far from the terminals where it was released before binding to its receptor. Activation of NK1 receptors increases intracellular calcium levels, which causes slow depolarization of projection neurons, thus promoting their excitability [1–4].

Many other peptides are present in primary nociceptors and have been shown experimentally to promote nociceptive transmission. These peptides include the calcitonin gene-related peptide (CGRP), somatostatin, neurokinin A, galanin, vasoactive intestinal peptide (VIP), and brain derived neurotrophic factor (BDNF). Information about the exact distribution of these peptides and their receptors is limited, and some can even produce antinociceptive as well as nociceptive effects, factors that make their exact physiological roles in pain transmission unclear [2–4].

Other Inhibitory Neurotransmitters in the Dorsal Horn

Opioid receptors (μ, δ, and κ) are expressed on primary nociceptor presynaptic terminals, projection neurons and excitatory interneurons. Endogenous peptide agonists for these G protein-coupled receptors, such as enkephalin and dynorphin, are released from terminals of inhibitory interneurons. Presynaptic opioid receptors inhibit $Ca_v2.2$ voltage-gated calcium channel, thus reducing release of the fast excitatory neurotransmitter glutamate from nociceptor terminals. Postsynaptic opioid receptors activate potassium channels, causing hyperpolarization and thus reducing the excitability of the postsynaptic neuron [1–4].

Noradrenaline and serotonin are released from the terminals of descending inhibitory axons that project to the dorsal horn from the locus coeruleus and nucleus raphe magnus in the brainstem. Noradrenaline acts on α_2-adrenergic receptors, while serotonin produces its analgesic effects via metabotropic serotonergic receptors such as 5-HT_1 and 5-HT_5. These α_2-adrenergic and serotonergic receptors are expressed by some primary nociceptors and excitatory interneurons and are coupled to inhibitory G proteins in these cells. Like opioid receptors, they inhibit neuronal activity through both presynaptic inhibition of fast neurotransmitter release and hyperpolarization of postsynaptic neurons [1–4].

Other receptor systems have been identified in the dorsal horn, many with receptors that are present on primary nociceptor terminals, that may also have inhibitory roles in pain transmission. These include metabotropic glutamate receptors, metabotropic GABA receptors ($GABA_B$), muscarinic cholinergic receptors, and cannabinoid receptors. In addition, there are other serotonergic receptors in the dorsal horn whose role is less well defined, as they are generally thought to be excitatory (the metabotropic 5-HT_7 and the ionotropic 5-HT_3 receptor). Their roles in inhibiting vs. facilitating pain transmission may depend on the cell types affected and/or whether these systems are studied in the setting of acute vs. chronic pain [1–4].

High Yield Points

- Glutamate is the main fast excitatory neurotransmitter in the dorsal horn. It binds to the ionotropic AMPA, kainate, and NMDA glutamate receptors.
- GABA and glycine are the main fast inhibitory neurotransmitters in the

dorsal horn. They bind to the ionotropic $GABA_A$ and glycine receptors, respectively.

- Many other neurotransmitters in the dorsal horn do not mediate fast synaptic transmission but still modulate synaptic function and neuronal activity. These transmitters are released from neurons, travel through the interstitial fluid, and bind to extrasynaptic receptors, often G protein-coupled receptors, on other neurons by "volume transmission".
- Substance P is an excitatory slow neuromodulator released from dense core vesicles in presynaptic terminals of peptidergic primary nociceptors. It binds to NK1 receptors on projection neurons and causes a G protein-mediated slow depolarization, enhancing nociceptive transmission.
- Endogenous opioid peptides such as enkephalin and dynorphin are released from inhibitory interneurons and activate μ-, δ-, and κ-opioid receptors present on both primary nociceptor terminals and their targets. These G protein-coupled receptors inhibit presynaptic release of glutamate and reduce the excitability of postsynaptic neurons through inhibition of presynaptic $Ca_v2.2$ voltage-gated calcium channels and activation of postsynaptic potassium channels, respectively.
- Norepinephrine and serotonin are released from terminals of descending inhibitory axons originating in the brainstem. Norepinephrine activates inhibitory α_2-adrenergic receptors, while serotonin activates a variety of 5-HT receptors including the inhibitory G protein-coupled $5\text{-}HT_1$ and $5\text{-}HT_5$. Other excitatory 5-HT receptors such as the G protein-coupled $5\text{-}HT_7$ and ionotropic ligand gated ion channel $5\text{-}HT_3$ may be involved in facilitation of nociception.

Questions

1. Examples of neurotransmitters mediating fast synaptic transmission in the dorsal horn include all of the following except
   A. Glutamate
   B. GABA
   C. Glycine
   D. Substance P
   Answer: D
2. Which of the following statements about Substance P is FALSE?
   A. It has strong inhibitory effects in the dorsal horn
   B. It is released from the terminals of peptidergic primary nociceptors
   C. It binds to the NK1 receptor, which causes a slow postsynaptic depolarization
   D. NK1 receptors are found on projection neurons in the dorsal horn
   Answer: A
3. Inhibitory neurotransmitters in the dorsal horn include all of the following except
   A. GABA
   B. Noradrenaline
   C. Enkephalin
   D. Morphine
   Answer: D

References

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