Glutamate Kainate Receptor in Pain Transmission and Modulation

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MAJOR CONTRIBUTIONS


MAIN TOPICS

Peripheral KA receptors in sensory transmission
Postsynaptic KA receptors mediate sensory nociceptive synaptic transmission
Presynaptic KA receptors regulate excitatory sensory transmission
Presynaptic regulation of spinal inhibitory transmission: a balance of excitatory vs. inhibitory influences
KA receptor desensitization dictates the time course of KA-triggered transmitter release
KA triggers release of both GABA and glycine
KA action occurs by an ionic mechanism
Synaptic glutamate triggers a KA and GABAB receptor-mediated suppression of spinal inhibitory transmission
A cellular mechanism for presynaptic KA receptor-mediated regulation of transmitter release
KA receptors and The Gate theory

SUMMARY

Glutamate is the major excitatory transmitter in the spinal cord dorsal horn. At postsynaptic sites, subtypes of glutamate receptors are important for mediating sensory synaptic responses. While AMPA and NMDA receptors are likely expressed in all sensory synapses, kainate(KA) receptors are expressed mainly in synapses receiving high-threshold sensory inputs.
In addition to its postsynaptic role, presynaptic KA receptors are important for regulation of both excitatory and inhibitory transmission within the dorsal horn. In the spinal cord dorsal horn, excitatory sensory fibers often terminate adjacent to sites of GABA and glycine release. Glutamate released from sensory fibers caused a KA and GABA$_B$ receptor-dependent suppression of inhibitory transmission in spinal slices, providing evidence for a new role of KA receptors in regulating sensory transmission. Genetic studies using selective KA subtype receptor knockout mice found that KA receptors are important for persistent inflammatory pain as well as emotional responses to pain.

INTRODUCTION

Glutamate is the major excitatory transmitter at primary afferent synapses, where it conveys sensory information to the central nervous system via postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-isoxazole propionic acid), NMDA (N-methyl-D-aspartate), and KA receptors on spinal cord dorsal horn neurons. In addition to postsynaptic receptors, many neurons express on their presynaptic terminals ionotropic receptors that are thought to regulate transmitter release, including receptors for transmitters as well as autoreceptors for the transmitter(s) released by the terminal itself. Much recent effort has focused on KA receptors as possible presynaptic regulators of transmission. In the hippocampus, for example, presynaptic KA receptor activation appears to reduce release of both glutamate and GABA (γ-aminobutyric acid). At primary afferent synapses in the spinal cord, in addition to the postsynaptic KA receptors that contribute to EPSCs evoked by high-threshold dorsal root fiber stimulation, there are KA receptors expressed presynaptically by dorsal root ganglion (DRG) neurons.

It is well-known that KA can depolarize a subset of dorsal root fibers. In addition, the electrophysiological properties of KA receptors were first described in acutely dissociated DRG neurons. Defining a physiological role for these receptors has gained progress, in part due to the development of selective agonists and antagonists as well as generation of gene knockout mice. In this chapter, I will focus on the possible roles of KA receptors in the spinal cord dorsal horn by focusing on three major areas: (i) peripheral roles of KA receptors; (ii) postsynaptic KA receptor mediated sensory synaptic responses; (iii) presynaptic modulatory roles of KA receptors; (iv) presynaptic KA receptors as a balance mechanism for excitatory and inhibitory transmission.

PERIPHERAL KA RECEPTORS IN SENSORY TRANSMISSION

Considering the high density of KA receptors in small-size DRG cells, it is predictable KA receptors also exists in peripheral sensory terminals. KA receptors, along with other ionotropic glutamate receptors, have been localized on subpopulations of unmyelinated and myelinated sensory axons in normal skin. Activation of these receptors results in nociceptive behaviors and contributes to inflammatory pain.

There is also evidence that peripheral KA receptors undergo upregulation after inflammatory injury. At 48 h following complete Freund’s adjuvant (CFA)-induced inflammation, the proportions of unmyelinated axons labeled for KA receptors were 48% as compared with 27% in the non-inflamed paw, suggesting that peripheral KA receptors may contribute to peripheral sensitization.

POSTSYNAPTIC KA RECEPTORS MEDIATE SENSORY NOCICEPTIVE SYNAPTIC TRANSMISSION

For many years, it is believed that excitatory synaptic transmission is mainly carried out by AMPA receptors in central sensory neurons. In the spinal cord dorsal horn, many studies using non-selective antagonists conclude that the roles of AMPA receptors, although KA receptor mediated, if any, are also blocked by this antagonist. The development of selective receptor antagonists and gene knockout mice permit reexami-