The Ouchless Kind: The Role of P2X4 Receptors in Pain Signaling

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I. Introduction

Apfelbaum (2003) states 80% of patients experience acute pain after surgery. Doctors are required to prescribe opiates after surgery to alleviate the severe pain. However, 25% of patients experience addiction to the opiate, increased pain and itching, among side effects. Nociceptors are pain-sensing neurons with receptors that respond to damaging or harmful stimuli and send those signals to the brain. The nociceptors come in two varieties: fast-conducting myelinated type A fibers, that transmit sharp pain, and non-myelinated type C fibers which conduct a slower pain signal for dull pain. Mechanical stimuli activate ion channels on sensory neurons, therefore opening them and allowing for positive ion influx. Propagation occurs through ligand-gated channels, such as P2X4, on the neurons. When stimuli are applied to the epidermis, touch and pain receptors send action potentials through the spinal cord up to the brain.

Figure 1.1 - Myelinated A fibers (upper) transmit fast signals due to the presence of myelin. The non-myelinated C fibers (lower) demonstrate a slower response due to the lack of myelin.

II. The perception of pain

The perception of pain is important to determine injury, however there are times when it is appropriate to block pain, such as post-surgery. To prevent opioid-related side effects, researchers have begun to look into localized treatment instead of treating the whole body. A target for pain reduction might be ion channels, such as P2X4, which are receptors present on nociceptive nerve terminals in the spinal cord and the periphery. They have been shown to be involved in pain perception. In the central nervous system, P2X4 is found equally on A and C fiber neurons and is the most highly expressed of the various P2X receptors.

III. P2X4 structure

P2X4 can be divided into two domains. The extracellular domain contains the ATP-binding region which is shown in steel blue. The transmembrane domain which contains the gate and the channel is shown in cyan. Hypothesized ATP-binding sites within the extracellular portion of the protein are shown in gold. The transmembrane stabilizers hold the alpha helices of the gate closed when not active and are shown in slate blue. When open, the gate, shown in orchid, allows for positive ions to enter the neuron to depolarize it. Leu340, shown in magenta, both stabilizes the transmembrane portion and is part of the gate. Gly350, shown in purple, changes the gate hinge position when ATP binds to the open channel.

Data indicate that P2X4 is connected to the perception and transmission of pain after nerve injury in the lumbar region. Tsuda, M., et. al. (2003).

IV. How P2X4 operates

ATP binding, which is required for activation, potentially occurs in the groove between A and B chains in each of the three subunits. Once bound, ATP causes a conformational change in the transmembrane portion, opening the channel. The open channel allows an influx of positive ions into the neuron, resulting in depolarization of the neuron and the transmission of pain.

V. Experimental data suggesting involvement of P2X4 in pain transmission

Data indicate that P2X4 is connected to the perception and transmission of pain after nerve injury in the lumbar region. Apfelbaum (2003) states 80% of patients experience acute pain after surgery. Doctors are required to prescribe opiates after surgery to alleviate the severe pain. However, 25% of patients experience addiction to the opiate, increased pain and itching, among side effects. Nociceptors are pain-sensing neurons with receptors that respond to damaging or harmful stimuli and send those signals to the brain. The nociceptors come in two varieties: fast-conducting myelinated type A fibers, that transmit sharp pain, and non-myelinated type C fibers which conduct a slower pain signal for dull pain. Mechanical stimuli activate ion channels on sensory neurons, therefore opening them and allowing for positive ion influx. Propagation occurs through ligand-gated channels, such as P2X4, on the neurons. When stimuli are applied to the epidermis, touch and pain receptors send action potentials through the spinal cord up to the brain.

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When painful stimuli are detected by receptors such as P2X4, pain signals are transferred from the spinal cord to the brain via sensory nerves. The stimulus causes P2X4 to open due to ATP binding, allowing an influx of positive ions which causes depolarization and signal transmission. Data indicated when P2X4 is blocked, the withdrawal threshold increases, meaning pain transmission is reduced. Since P2X4 initiates the pain signal, blocking the initiation at the periphery would block the pain signal from getting to the brain. This ultimately eliminates the need for systemic opiates and the negative side effects.

VI. Conclusions

The perception of pain is important to determine injury, however there are times when it is appropriate to block pain, such as post-surgery. To prevent opioid-related side effects, researchers have begun to look into localized treatment instead of treating the whole body. A target for pain reduction might be ion channels, such as P2X4, which are receptors present on nociceptive nerve terminals in the spinal cord and the periphery. They have been shown to be involved in pain perception. In the central nervous system, P2X4 is found equally on A and C fiber neurons and is the most highly expressed of the various P2X receptors.

References


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