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Specific Quality of Sensation Derived from the Pain-Spots

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Abstract

The most common type of cannabinoid is the tetra-hydrocannabinol, which is one of the major psychoactive components isolated from Cannabis sativa. Cannabinoids can bind to Gi-protein coupled cannabinoid type 1 receptors, which is highly expressed in the pre- and post-synaptic in brain and spinal cord, as well as the Gi-protein-coupled cannabinoid type 2 receptors that is predominantly located in the immune system. The activation of CB1 and CB2 inhibits the formation of intracellular cAMP, hence leading to a tremendous reduction of the excitatory effect within the neurons.

Keywords: Cannabinoid; Pain sensation; Receptors; Neurokinin; Spinal cord; Pain pathway

Introduction

In addition, the activation of CB2 can further prevent the mast cell degranulation and the release of pro-inflammatory mediators, making the reduction in pain sensation even more drastic and effective.NE is the principal neurotransmitter of the adrenergic pathways and is synthesized from phenylalanine in the nerve terminals. Phenylalanine is converted into tyrosine and then into 3,4-dihydroxyphenylalanine by tyrosine hydroxylase. DOPA is then further converted into dopamine, which is the precursor of NE that is stored in the vesicles of the nerve terminals. The receptors of NE include α1-Gqα-, α2-Giα-, β-Gsα-protein-coupled receptors. α1-Gqα- and β-Gsα-protein-coupled receptors are predominantly located in postsynaptic neurons, whereas α2-Giα-protein-coupled receptors are located in presynaptic neurons [1]. Thus, the activation of the α2-Giα-protein-coupled receptors inhibits the Ca2+ influx, and causes the reduction of NE release out from the synapse. On the other hand, the binding of NE with α1-Gqα- and β-Gsα-protein-coupled receptors that are located in the postsynaptic neurons stimulates the PLC/PKC and cAMP/PKA signaling pathways, respectively, and causes excitatory effects.

Discussion

Understanding the complex mechanisms of pain is undoubtedly essential for pain research and pain management. Hence, the present review was comprehensively discussed based on the molecular and cellular mechanisms underlying the pain pathway as a whole picture. Moreover, the major types of neurotransmitters involved in the pain transduction, transmission and modulation have been completely elaborated along with their locations and eventual pharmacological effects. This could enlighten the understanding of the global scientists towards the pain topic and provide a useful guide for continue analgesic drug discovery in future. Tachykinins is the largest family of neuropeptides [2]. There are three members of tachykinins family involved in the neurogenic-induced inflammation, which are SP, neurokinin A and neurokinin B. These neuropeptides are produced from peripheral terminals of the sensory nerve fibers, such as muscle and skin via proteolytic cleavage of their precursor, pre-protachykinins. The SP, NKA and NKB selectively bind to their cognate receptor according to their affinity to these receptors. For a clearer picture of the receptors that are compatible with the neuropeptides, SP binds to neurokinin type 1 receptor while NKA binds to neurokinin type 2 receptor and NKB binds to neurokinin type 3 receptor receptors, respectively. All these receptors are Gq-protein coupled receptors, which mediate through PLC/IP3 and DAG/PKC signalling pathways upon activation, hence resulting in its excitatory effects. CGRP is widely produced in both central and peripheral nervous systems; however, it is primarily located in the primary afferent nerves. As a direct derivative of the DRG, CGRP is found in the DH of the spinal cord and associated with the conduction of noxious stimulation. CGRP is related to the excitatory effects of SP, which results in Ca2+ release [3]. The receptors of CGRP are Gs-protein-coupled, which are known as calcitonin receptor-like receptor located in the nucleus accumbens, indicating that the CNS controls the CGRP-mediated pain transmission. BK is a well-known algogen and acts as one of the inflammatory mediators that are locally produced from the breakdown of high-molecular-weight kininogens in the site of the inflamed tissue. In the nociceptive afferent nerve fibers, BK binds to Gq-protein-coupled bradykinin receptor type B1 or bradykinin receptor type B2 receptors, leading to sensitization. The activation of B1 orB2 receptors causes activation of the PLC to break down the phosphatidylinositol 4,5-bisphosphate into IP3 and DAG, and subsequently, DAG activates the PKC, leading to the increase of Ca2+ conductance. Furthermore, BK can act synergistically with other algogenic substances, such as PG and NGF, to further stimulate the production of pro-inflammatory cytokines [4]. It can also further sensitize the nociceptors, such as interleukin-2, 5-HT, histamine and prostanoids, to heat. During the degranulation of the inflammation-induced mast cell, the PAF is stimulated for release and subsequently induces the production of serotonin or 5-HT from the circulating platelets. It is an indolamine mediator, which causes extravasation of plasma and hyperalgesia in human and rats. The 5-HT receptors are located on the nerve cells membrane and all of these receptors are GPCRs except the 5-hydroxytryptamine type 3 receptors, which is ligand-gated ion channel [5]. Two major types of 5-HT receptors present on the sensory neuron's terminal are 5-hydroxytryptamine type 2A receptor and 5-HT3. 5-HT2A receptors are Gq-protein-coupled, which enhances the pain sensation through PLC/IP3 and DAG/PKC pathways, whereas the activation of the 5-HT3 receptors induces a

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depolarization current, hence causing excitatory effects to be produced. In addition to 5-HT3, histamine is one of the well-known products of mast cell degranulation, which reacts with its Gq-protein coupled receptor located at the afferent nerve terminal, aiding in the inflammation process. Additionally, other cytokines, such as interleukin 1β and tumour necrosis factor α, play a crucial role in exerting a powerful pro-inflammatory effect that causes hyperalgesia, as well as in exerting a synergistic interaction upon contact with NGF. PG is produced from the AA via the catalysis of COX. They can be found in other tissue in our bodies and are considered as an archetypal sensitizing agent that reduces the nociceptive threshold as well as the core cause of tenderness. PGE2 and prostacyclin are two major prostaglandins that lead to a direct afferent sensitization. The receptor of PGE2 can be divided into 4 major types, such as prostaglandin E2 receptor type 1–4, whereas the receptor of PGI2 is termed prostacyclin receptor. EP1 is Gq-protein coupled receptor, which leads to the PLC/IP3 and DAG/PKC signalling pathway, EP2, 4 and IP are Gs-protein-coupled receptors, which act on promotion of the AC/cAMP/PKA signalling pathways upon activation, whereas EP3 is a Gi-protein-coupled receptor, which leads to inhibitory effects. In addition, PG enhances the effects of other chemical mediators, such as 5-HT and BK, as well as augments the neuropeptide, such as SP and CGRP, to be released. In other words, the increase of the BK induces the PG to be released and results in a self-sensitizing effect [6]. LTB4 is one of the eicosanoid inflammatory mediators that are produced within the leukocytes. Upon injury caused by mechanical or thermal stimuli, the AA is broken down into 5-hydroperoxyicosatetraenoic acid by lipooxygenase, and is subsequently hydrolyzed into LTB4 by leukotriene A4 hydrolase. LTB4 is mainly responsible for recruiting neutrophils towards the site of the damaged tissue, whilst simultaneously promoting the production of cytokines. In the presence of poly-morphonuclear leucocytes, LTB4 can indirectly cause hyperalgesia probably through the afferent terminal pathway. LTB4 can cause sensitization of the nociceptors by increasing the cAMP/PKA activities [7]. Some animal studies have speculated that the accumulation of inflammation-induced neutrophil is highly associated with the increasing number of LTB4, which causes the indirect stimulation of hyperalgesia. The site of injury is often more acidic than homeostasis, and hence the local content of protons shows a hike in number. The increasing number of these protons activates both the acid-sensing ion channels and VR1 around the injury location. ASICs are neuronal voltage-insensitive Na+ channels, which are activated by extracellular protons. Typically, these channels respond to a low pH surrounding and are suggested by studies to be involved in the modulation of our bodies' mechano-sensation [8]. Furthermore, there was research indicating the exposure of primary afferent nerve fibers to a pH lower than 6 can stimulate the ASICs. VR1 can also be activated by these protons via either heat stimuli or capsaicin. VR1′s location in the dorsal roots of primary afferent nerves makes it mainly responsible for detection and regulation of the body's temperature, thus providing a burning sensation when stimulated by heat. Upon the activation of both the VR1 and ASICs, the presence of BK, PGE2 and histamine at the injury site can further increase the intracellular Ca2+ influx, hence enhancing the expression of VR1 and sensory neuron-specific (SNS) Na+ channels. Subsequently, the influx of the Na+ generates an action potential, thus causing sensitization of the afferent nerves. Although the rise of the intracellular Ca2+ leads to the release of the SP and CGRP, it can desensitize VR1.ATP is an important intracellular messenger that is released locally by the damaged tissues and directly stimulates its receptors [9]. This occurs when ATP is metabolized into adenosine by ectonucleotidases and binds to its receptor, ionotropic purino receptors that are located at the peripheral site of the sensory neurons and centrally on the second-order neurons in the DH. In general, there are six types of P2X receptors, including P2X1–6 expressed in the sensory neurons. Amongst these six types, purino receptor type 3 receptors are one of the most selectively expressed receptors in the small C-fibered nociceptor [10].

Conclusion

Once the ATP binds to the P2X3 receptors, Na+ can cross these channels and induce membrane depolarization, hence activating various Ca2+-sensitive intracellular processes and causing both pain and hyperalgesia. ATP can pre-synoptically act on the nociceptors to increase the release of glutamate. On the other hand, ATP produces a by-product from its metabolism, adenosine, which binds to either adenosine type 1 receptor Gi-PCRs for inhibitory action or binds to the adenosine type 2 receptor Gs-PCRs that are located peripherally and centrally to sensitize the nociceptors via the cAMP/PKA signalling pathways.

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Conflict of Interest

None.

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