Herbal Compounds: Important Role as TRPV1 Channel Modulator in Pain Sensation

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Abstract
Ion channels play a significant role in pain perception. Among them, transient receptor potential cation channel subfamily V member 1 (TRPV1) expressed in dorsal root ganglia (DRG) neurons plays a pivotal role. Considering the potential side effects and high risk of dependence from opiates commonly co-prescribed with non-steroidal anti-inflammatory drugs (NSAIDS), alternative compounds from plants need to be identified. For years, herbal medicines treated pain worldwide, but their precise action was not clear until recently. The role of individual ion channels in pain detection and transmission can be separated and understood better now than ever before. Additionally, through improvements in active compound purification techniques and alteration of active compounds by synthetic chemistry, many herbal and naturally derived compounds are waiting to be screened for their probable role as analgesic. In this small review, some very familiar plant-based compounds, which act on TRPV1 channels and in turn influence pain sensation, are discussed.

Keywords: dorsal root ganglia (DRG), herbal medicines, ion Channels, pain pathway, transient receptor potential cation channel subfamily V member 1 (TRPV1)

Introduction

Pain is an unpleasant sensory and emotional experience that affects estimated 86 million American adults to some degree. Morphine is still the most widespread pain reliever for severe pain management, but it possesses a high potential for addiction and negative side effects such as respiratory issues, constipation, or diarrhea. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen that-mainly target and block cyclooxygenase (COX) enzyme activity for the management of pain and inflammation are commonly combined with opiate pain killers. These drugs help limit the minimum effective opiate dose in treating pain, but their frequent use could cause adverse effects including gastrointestinal bleeding and ulceration, impaired renal function, and inhibition of platelet aggregation. Finding pain remedies from plant-based products is an ancient process. Since several hundred years ago in ancient Egyptian, Ayurveda (Indian) and Chinese traditional medicine, various extracts of natural products, mostly plants, were used as analgesics, even if their modes of action were not clear. With the discovery of new targets such as receptors and ion channels , modern medicine uses various plant-based purified products as medicine (Vriens, Nilius et al. 2008). Ancient medicines acted on peripheral sensory neurons by blocking their ability to detect painful stimuli, leading to the treatment and analgesia of many maladies, including toothache or arthritic pain. Due to today's remarkable plant-based active compound purification techniques, it's known how ancient medicine worked on sensory neurons.

An ideal plant based analgesic would be one which acts specifically on "pain-sensing" nerves, not on the central nervous system or respiratory system, inexpensive to be administered with longer analgesic effect retention capacity, so that the patient does not get addicted due to its chronic use (Schumacher 2010).

Role of nociceptors and primary afferent fibers in pain

Nociceptors are specialized sensory neurons that express specialized proteins in their nerve terminals and are capable of pain transduction. The cell bodies of nociceptors reside in dorsal root ganglia, which innervate the trunk, limbs, and viscera and project centrally to the spinal cord dorsal horn (Caterina and Julius 2001). This is often the first step in the process called nociception and causes the perception of pain. The essential function of nociceptors is to transduce noxious stimuli (mechanical, thermal and chemical) into depolarization which in turn triggers action potentials, to conduct these action potentials from the peripheral sensory site to the synapse in the central nervous system, and converting them into neurotransmitter release at the presynaptic terminal. All these events need ion channels (McCleskey and Gold 1999). Nociceptors are distributed throughout the body except the brain parenchyma. Nociceptors are different from peripheral neurons as they are relatively small in size, and are either unmyelinated (C-type) or thinly myelinated (Aδ type)(Schumacher 2010).

Ion channels in DRG neurons

Dorsal root ganglia contain the cell bodies of nociceptors that transmit pain signals of mechanical, thermal or chemical origin from the periphery to their corresponding spinal synapses through the currency of action potential and neurotransmitter release. TRPV1 is normally expressed throughout the nociceptive pathway of peripheral nervous system, small to medium size DRG neurons, laminae I and II of dorsal horns and small-diameter axons of dorsal roots (Lauria, Morbin et al. 2006).

Besides that, voltage gated Na^+ and Ca^{2+} channels, ASIC, ligand gated ion channels, P2X, NMDA, AMPA, and Kainate receptors are some of the important ion channels expressed in the periphery and DRG neurons. They are crucial for pain sensation (Eglen, Hunter et al. 1999). TRPV1 is expressed in small sensory neurons (Caterina, Leffler et al. 2000; Zacharova and Palecek 2009) and attracted attention as molecular target of pain pathway (Szallasi and Appendino 2004; Szallasi, Cortright et al. 2007). To restrict our discussion, in this short review, we will focus on TRPV1 channels expressed in the peripheral nervous system, DRG neurons and significance of plant-based active metabolic compounds in modulation of TRPV1 channels towards their analgesic role.

Natural Products influence pain pathway

Capsaicin

Natural compounds from plants, herbs, and spices are the most powerful and important tools in manipulating the key proteins like TRPV1 ion channels in pain pathways. Capsaicin is one of those unique irritant active compounds of Chilli peppers (a secondary metabolite responsible for their zing) that robustly and selectively excites primary afferent sensory neurons (Jancso, Kiraly et al. 1977). Nociceptors are partially characterized by their sensitivity to capsaicin, a product of capsicum peppers that is also the active compound of many 'hot' and spicy foods (Caterina, Schumacher et al. 1997) .
Structurally, capsaicin contains a vanillyl group with a hydrophobic hydrocarbon tail. Being small and hydrophobic, capsaicin crosses the plasma membrane readily to reach an intracellular ligand-binding site on TRPV1 channel and causes channel activation and cation permeation.

Ginseng

Ginsenosides are also known as panaxosides. They are the class of steroid glycosides, and triterpene saponins, found exclusively in the plant genus Panax (ginseng). Ginsenoside Rg1 (GRg1), one of the major active constituents of *Panax notoginseng* was found to be anti-inflammatory and antinocioceptic by acting as an antagonist of TRPV1 channel, similar to capsazepine (Huang, Ding et al. 2012). Intrathecal injection of ginsenosides attenuated

bone cancer-related pain behavior in adult male C3H/HeJ mice (Yoon, Kim et al. 2010).

Cannabinoids

Cannabinoids are naturally occurring and most diverse compounds found in the *Cannabis sativa* plant, which act on cannabinoid receptors on cells that repress neurotransmitter release in the brain. Of over 480 different compounds present in the plant, only around 66 are termed cannabinoids. Cannabinoids can directly inhibit peripheral capsaicin-sensitive nociceptive neurons by dephosphorylating and desensitizing TRPV1 via a calcium calcineurin-dependent pathway (Patwardhan, Jeske et al. 2006). Cannabinoid receptor type 1 (CB1), which are present in the nervous systems (Manzanares, Julian et al. 2006), induced inhibition of TRPV1 channel activation, thus providing a therapeutic option to deal with inflammation and pain (Yang, Yang et al. 2013). CB1 receptors are present in the nervous system areas involved in modulating nociception and evidence supports a role of the endocannabinoids in pain modulation.

Garlic

Allicin is an organosulfur compound obtained from garlic, known for its numerous antimicrobial properties and remedies against pain and arthritis. Allicin is found to be an activator of TRPV1 current in capsaicin-sensitive but not insensitive DRG neuron (Macpherson, Geierstanger et al. 2005; Vriens, Appendino et al. 2009). Sulpher-containing diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) are volatile compounds produced in garlic bulb that act as TRPV1 agonists (Koizumi, Iwasaki et al. 2009).

Pepper

Piperine is the alkaloid responsible for the pungency of black pepper and long pepper. Capsaicin and piperine cause activation of the heat and acidity sensing TRPV1 channels on pain sensing nerve cells. Piperine is less potent but more efficacious when tested in heterologously expressed human recombinant TRPV1 channels in HEK-293 cells (McNamara, Randall et al. 2005). Piperine is also known for its traditional value in Chinese medicine, and it is used as an anti-inflammatory in digestion (Vriens, Nilius et al. 2008).

Turmeric

Curcumin is the principle natural phenol product present in turmeric, responsible for the yellow color. Turmeric, which is extensively used as a popular spice in south-eastern Asian food, is also believed to have analgesic effects. Curcumin was found to act as an antagonist on capsaicin induced TRPV1 current (Yeon, Kim et al. 2010; Lee, Shin et al. 2013), which in turn inhibits TRPV1-mediated pain hypersensitivity. Curcumin as a chemo-preventive agent, inhibits the expression and activity of COX-2 in several different gastrointestinal cell lines (Zhang, Altorki et al. 1999).

Mustard

Allyl isothiocyanate (AITC or mustard oil) is a natural pungent compound found in mustard, known for its medicinal values (Rask, Andreasson et al. 2000). A study in TRPA1 knockout mice indicates that allyl isothiocyanate directly activates TRPV1(Gees, Alpizar et al. 2013) current in a TRPA- independent manner (Alpizar, Boonen et al. 2014).

Conclusion

There is a constant search for competitive vanilloid antagonists by the pharmaceutical industries due to the unquestionable involvement of the TRPV1 receptor in pain transduction. Plant-based active compounds play an important role as analgesics and may prove to be less harmful in side-effects and addictive potential compared with current treatments. Biologists and synthetic chemists have an exciting new domain of research: finding out or modifying the structures of active compounds from herbal sources that show analgesic

properties. In the effort to make a very specific TRPV1 antagonist, promising compounds from *in vitro* and *in vivo* studies can be tested in further behavioral studies. This research may produce pipeline of promising compounds for analgesic drug discovery.

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