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Control of pain with topical plant medicines

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PEER REVIEW

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ABSTRACT

Pain is normally treated with oral nonsteroidal anti-inflammatory agents and opioids. These drugs are dangerous and are responsible for many hospitalizations and deaths. It is much safer to use topical preparations made from plants to treat pain, even severe pain. Topical preparations must contain compounds that penetrate the skin, inhibit pain receptors such as transient receptor potential cation channels and cyclooxygenase-2, to relieve pain. Inhibition of pain in the skin disrupts the pain cycle and avoids exposure of internal organs to large amounts of toxic compounds. Use of topical pain relievers has the potential to save many lives, decrease medical costs and improve therapy.

1. Introduction

Pain can be difficult to treat, especially chronic pain. Fibromyalgia, neuropathic pain and chronic back pain are routinely treated with oral opioids, such as hydrocodone and oxycodone. A recent systematic review found no convincing evidence that oxycodone is of value in pain treatment from fibromyalgia, diabetic neuropathy, postherpetic neuralgia or neuropathic pain[1]. Osteoarthritis pain is frequently treated with oral nonsteroidal anti-inflammatory drugs (NSAIDs). When the NSAIDs are inadequate for pain control in osteoarthritis or rheumatoid arthritis, stronger agents are used such as corticosteroids, hydroxychloroquine, sulfasalazine, leflunomide, auranofin, etanercept, infliximab, anakinra and methotrexate. This is called the Carpenter approach[2]. If the hammer does not work, get a bigger hammer. All of these agents have serious adverse effects. Methotrexate can kill patients if an excessive dose is used.

Of course, NSAIDs were discovered based on the structure of aspirin, a monoterpenoid, which comes from meadowsweet, *Filipendula ulmaria*. Opioids are alkaloids that come from the opium poppy, *Papaver somniferum*. The problem with these agents is that large doses are taken orally or by injection, travel throughout the body and have toxic effects where they are not needed. NSAIDs are used in chronic pain conditions, but are not effective for most patients[3]. NSAIDs cause 100 000 ulcers in the USA every year according to the Centers for Disease Control. Of these, 10 000 patients die. NSAIDs also damage the kidneys and have other adverse effects. Opioids cause seizures and respiratory depression. They cause 14 000 deaths every year in the USA according to the Centers for Disease Control. They also cause addiction and tolerance such that after a couple of weeks, patients have to increase the dose to get any pain relief.

This review will point out that there is a better way to treat pain than by giving large oral doses or injections to treat pain in the brain and brain stem. Liniments and other topical preparations can be used that are applied in small amounts to the skin where they are needed. Analgesic molecules in the preparations penetrate the skin in small but sufficient amounts, act where they are needed and are rapidly cleared from the skin and the body.

2. What is the pain cycle

There is a pain cycle in the body that starts with pain receptors on

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sensory afferent neurons of the skin. These are small unmyelinated (C-type) or thinly myelinated (A delta-type) nerves. The sensory afferents have a pseudo-unipolar morphology[4]. A common axonal stalk sends axons to the skin and to the brain stem where they synapse with ascending neurons that communicate with the hippocampus, hypothalamus and other brain regions. This pseudo-unipolar morphology may be important in reflex amplification of the pain cycle. The brain neurons communicate with descending neurons that synapse with neurons in the brain stem. These descending brain stem neurons have terminals in the skin that are neurotrophin secreting[5]. Activation of the pain cycle can magnify pain in the body.

Sensory afferent neurons contain a number of different pain receptors. These pain receptors are activated or inhibited by various natural substances such as histamine that are made in the skin, work in the skin, and do not persist for very long in the skin.

These neurons are also regulated by input from the brain stem and the brain. The most abundant pain receptors in the skin are located on sensory afferent neurons and are called transient receptor potential (TRP) cation channels. These channels are usually made up of six membrane spanning units and a central cation permeable channel. Some TRP channels are also located in the brain and the brain stem. These receptors form a family of receptors that respond to heat, cold, mechanical stress and other painful stimuli. TRP channels have a characteristic of opening in response to an agonist, which then results in inhibition. In other words, agonists and antagonists can have the same long term effects, pain inhibition. TRP channels are not all expressed in the same skin afferent neurons. There are distinct neuronal populations that express the various TRP channels[4]. It is convenient to describe these receptors in terms of the agonists and antagonists that interact with them.

The canonical TRP subfamily TRPC, has at least 7 members[6], which tend to be activated by diacylglycerol. Phospholipase C makes diacylglycerol, which is an endogenous compound.

The vanilloid subfamily, TRPV, has 6 members and tends to be activated by heat[6]. However, TRPV4 can be activated by swelling caused by 5',6'-epoxyeicosatetrienoic acid, an endogenous compound. Capsaicin is an agonist for TRPV1. Activation of the channel by capsaicin causes pain, results in later inactivation of the channel and relief of pain. Eugenol and gingerol are monoterpenoid agonists for TRPV1[7]. This channel is activated by endovanilloids, cannabinoids, endocannabinoids, hydroperoxyeicosatetraenoic acid (HPETE), hydroxyeicosatetraenoic acid (HETE) and other compounds[6]. Endovanilloids, endocannabinoids, HPETE and HETE are made in the skin, act in the skin and are quickly cleared from the skin. Bradykinin and ATP sensitize TRPV1 by stimulating protein kinase C_ε dependent phosphorylation to greatly increase pain[8]. Lidocaine activates TRPV1, whereas isoflurane, enflurane, sevoflurane and desflurane sensitize TRPV1 can increase pain[7]. Dynorphins and adenosine are TRPV1 antagonists in the brain[7]. Histamine and several prostaglandins potentiate the activity of TRPV1, greatly increasing pain and itch[9]. TRPV2 is activated, then inhibited, by cannabidiol and tetrahydrocannabinol[7]. The monoterpenoid, citral, inhibits TRPV2[7]. TRPV3 is activated by camphor, thymol, eugenol, carveol, carvacrol, borneol, menthol, and all plant-derived monoterpenoids[6,10]. TRPV4 is activated by endocannabinoids, arachidonic acid metabolites, the diterpenoid bisandrographolide A, and is inhibited by the monoterpenoid citral[7]. TRPV5 and TRPV6 are less well characterized. TRPV5 can be inhibited by econazole[7].

The melastatin subfamily, TRPM, has several members[6]. TRPM1 is activated by steroids[9]. The TRPM2 receptor is activated by ADP-ribose, cyclic ADP-ribose, hydrogen peroxide and heat[6]. The TRPM3 receptor is activated by sphingosine. TRPM4 and 5 are activated by heat. TRPM8 is activated by cold, menthol and icilin. ADP-ribose, cyclic ADP-ribose, hydrogen peroxide and sphingosine are endogenous compounds that are made in the skin, act in the skin and can be quickly cleared from the skin.

The ankyrin subfamily, TRPA, has one member. TRPA1 responds to allicin, isothiocyanates, cannabinoids, cinnamaldehyde and arachidonic acid[6]. Arachidonic acid is an endogenous compound that is made in the skin, acts in the skin and is quickly cleared from the skin. The A and J series of prostaglandins activate the channel[9]. TRPA1 also responds to methyl salicylate, isoflurane and lidocaine[4,7].

The polycystin subfamily, TRPP, has three members[6]. They tend to respond to mechanical stress and calcium. The mucolipin subfamily TRPML has three members[6]. This family is not well characterized, appears to be located on lysosomal membranes and may respond to protons.

All TRP channels are calcium channels[6]. Some are permeable to other cations as well such as Na^+ and Mg^{2+}. If TRP channels open too much, excessive calcium may enter the sensory nerve terminal and activate apoptosis mechanisms[11]. This apoptosis is an essential component of pain control. The nearby nerve growth factor secreting efferent terminals may facilitate the recovery of the apoptotic afferent terminals.

Cannabinoids and endocannabinoids interact with cannabinoid receptors (CB) CB1 and CB2 to induce peripheral and central pain sensitization[12]. The endocannabinoids are endogenous, made locally, act locally and have short half lives. These compounds include 2-arachidonyl glycerol and anandamide. They also act on TRP channels as discussed above.

Lipoxins are endogenous compounds made from arachidonic acid and interact with ALX receptors (ALX/formyl peptide receptor 2, lipoxin A_4 receptor, resolvin D1 receptor) to cause pain. They are made locally, act quickly and do not persist in the skin. Lipoxins exist in a balance with resolvins, which are also made from arachidonic acid and relieve pain[13]. Resolvins interact with a number of receptors including ALX, GPR32 (G protein coupled receptor 32, resolvin D1 receptor, lipoxin A_4 receptor), ChemR23 (CMKLR1, chemokine like receptor 1, resolvin E1 receptor) and leukotriene B(4) receptor (BLT1). Resolvins also inhibit TRPA1, TRPV3 and TRPV4 to stop the pain cycle[14].

Opioid receptors are involved in processing pain centrally. The μ, δ, κ and nociceptin receptors are important in pain control,