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Specialized Pro-Resolving Mediators as Resolution Pharmacology for the Control of Pain and Itch

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Abstract

Recent progress in pain research indicates distinct mechanisms underlying the pathogenesis and resolution of pain. Specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, are endogenous lipid mediators that are synthesized from omega-3 polyunsaturated fatty acids during the acute phase or resolution phase of inflammation. SPMs possess broad safety profiles and exhibit potent actions in resolving inflammation in preclinical and clinical models. Accumulating evidence in the past decade has demonstrated powerful analgesia of exogenous SPMs in rodent models of inflammatory, post-operative, neuropathic, and cancer pain. Furthermore, endogenous SPMs are produced by sham surgery and neuromodulation such as vagus nerve stimulation, spinal cord stimulation, and electroacupuncture. SPMs produce their beneficial actions through multiple GPCRs, expressed by immune cells, glial cells, and neurons. Notably, loss of SPM receptors such as GPR37 impairs the resolution of inflammation and pain. I also highlight the emerging role of SPMs in the control of itch. Pharmacological targeting of SPMs or SPM receptors has the potential to lead to novel therapeutics for pain and itch as emerging approaches in “resolution pharmacology”.

Keywords

Neuroimmune modulation; nociceptive sensory neurons; neuroprotectin; omega-3 polyunsaturated fatty acids; resolvins; TRP channels

INTRODUCTION

Molecular and cellular mechanisms underlying the pathogenesis of pain have been extensively studied in the last two decades (1, 2). Pain is sensed by nociceptive sensory neurons (nociceptors), with cell bodies located in the dorsal root ganglion (DRG) and trigeminal ganglion, peripheral axons terminated in the skin, muscle, joint, and gut,

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and central axons terminated in the spinal cord and trigeminal nucleus (3) (Figure 1). (Nociceptors can be activated by physical stimuli, such as noxious thermal and mechanical stimuli through specific molecular sensors, such as transient receptor potential subtype V1, V4, A1, and M8 (TRPV1, TRPV4, TRPA1, TRPM8) and Piezo for sensing heat, cold, and mechanical pain, respectively (4-8). Nociceptors are also activated by chemical stimuli, including various inflammatory mediators (IFMs) (9). Pain is one of five cardinal symptoms of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (increased heat), *dolor* (pain), and *functio laesa* (loss of function).

IFMs activate nociceptors through receptive receptors for prostaglandin E2, proinflammatory cytokines and chemokines (e.g., IL-1β, TNF, IL-17, and CCL2), and ATP (1, 10-12). Furthermore, nociceptors express pattern recognition receptors such as toll-like receptors (TLRs) and STING (stimulator of interferon-gene) that can sense danger signals, such as RNAs and DNAs to elicit pain, itch, and analgesia (13, 14). IFMs directly activate nociceptors to produce spontaneous pain and further increase the sensitivity of nociceptors, leading to peripheral sensitization via modulation of ion channels that include voltage-gated sodium channels (Nav1.7, Nav1.8, Nav1.9) and TRP channels (e.g., TRPA1 and TRPV1, Figure 1), Peripheral sensitization also requires the activation of protein kinases, such as mitogen-activated protein kinases (MAPK) (15-18).

Central sensitization occurs in the central nervous system (CNS) and is triggered by the activation of NMDA receptors and extracellular signal-regulated kinase (ERK), a MAPK family member (19, 20). Central sensitization regulates chronic pain and widespread pain (21, 22). Loss of inhibitory synaptic transmission (disinhibition) is a critical feature of central sensitization. Peripheral sensitization typically precedes central sensitization, but central sensitization may send descending signals to sustain peripheral sensitization (22, 23). Recent studies suggest that neuroinflammation plays a crucial role in sustaining chronic pain (10). In addition to infiltration of immune cells to the peripheral nervous system (PNS) and CNS, neuroinflammation is characterized by activation of glial cells, such as satellite glial cells and Schwann cells in the PNS and microglia and astrocytes in the CNS (10, 24). Painful insults such as nerve injury, surgeries, arthritis, and cancer result in reactive changes in glial cells (25). Following activation, glia produce and release many powerful neuromodulators, such as TNF, IL-1β, IL-17, CCL2, CXCL1, and BDNF, in part through activation of MAPK signaling pathways (e.g., ERK, p38, and JNK pathways) and modulation of TRP channel function, as TRPV1 and TRPA1 are also expressed at presynaptic terminals of nociceptors (Figure 1). Glia-produced cytokines and BDNF potentiate excitatory synaptic transmission and further suppress inhibitory synaptic transmission in the pain neurocircuit to drive central sensitization and pathological pain (26-28).

A major advance in inflammation research is the realization that the resolution of acute inflammation is an active biochemical process, and accordingly, “resolution biology” and “resolution pharmacology” represent a new therapeutic frontier for the control of inflammation (29, 30). In 2011, emerging roles of resolvins in the resolution of inflammation and pain were proposed (31). Interestingly, certain anti-inflammatory treatments, such as inhibitors of cyclooxygenases, may delay the resolution of inflammation

(29, 32). Different types of immune cells have been implicated in the resolution of pain. For example, macrophages resolve inflammatory pain and infection-induced pain via phagocytosis and production of anti-inflammatory cytokines (IL-10 and TGF-β1) (33, 34). CD8+ T cells have been shown to resolve neuropathic pain after chemotherapy via IL-10 production (35). Bone marrow stromal cells resolve chronic arthritic pain and neuropathic pain via opioid receptor and TGF-β1 signaling (36, 37). A failure in the resolution process can lead to a transition from acute pain to chronic pain (31, 38).

Work by Serhan and collaborators has demonstrated that resolution of acute inflammation is an active process and requires the production of lipid-derived specialized pro-resolving mediators (SPMs), which are generated during the resolution phase of inflammation and contribute to the resolution process (39, 40). SPMs belong to a rapidly expanding family of molecules that are derived from ω-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The SPM family includes resolvins (RvD1-RvD6), protectins/neuroprotectins (PD1/NPD1) and maresins (MaR1, MaR2, and eMaR), cysteinyl-SPMs (MCTR1-R3, PCTR1-R3, and RCTR1-R3), as well as n-3 docosapentaenoic acid (DPA)-derived SPMs (PD1n-3 DPA). Additionally, SPMs consist of ω-6 arachidonic acid-derived lipoxins, such as lipoxin A4 and lipoxin B4 (LXA4 and LXB4) (41) (Figure 2). SPMs exert remarkable protective effects in animal models of certain human diseases, such as arthritis, kidney injury, infection, sepsis, and cancer, as well as periodontal, dry eye, and Alzheimer's diseases (31, 41-45). Notably, sham surgery produces acute pain and increases serum levels of RvD1 in the recovery phase (46). In this article, I review an increasing body of evidence demonstrating the potent biological actions of SPMs in the control of pain and itch (Table 1). I also highlight immune / glial modulation (Figure 3) and neuromodulation (Figure 4) as underlying mechanisms by which SPMs regulate pain and itch. Special emphasis has also been on pharmacological targeting of SPMs or SPM receptors for the development of novel therapeutics for pain and itch.

ROLE OF EXOGENOUS SPMs IN PAIN CONTROL

Local and systemic application of exogenous SPMs have been shown to alleviate pathological pain following tissue and nerve injuries via peripheral and central actions. These injuries are associated with inflammatory, postoperative, neuropathic, and cancer pain (Table-1).

Inflammatory Pain

Inflammatory pain manifests as spontaneous pain (licking, lifting, and biting the affected paw in experimental animals) and evoked pain, including mechanical hyperalgesia (increased response to painful stimuli), mechanical allodynia (painful response induced by previously innocuous stimuli), and thermal pain (heat hyperalgesia). Inflammatory pain is typically treated using nonsteroid anti-inflammatory drugs (NSAIDs), such as inhibitors of cyclooxygenases (COX1/2). While COX-1 is constitutively expressed, COX-2 is inducible after inflammation and drives inflammatory pain through peripheral and central modulation (47-50). COX-2 inhibitors are relatively safe but can produce gastrointestinal side effects (51). Using a rat model of pleurisy, Gilroy and coworkers demonstrated the

paradoxical effects of the COX-2 inhibitor NS-398: it reduced inflammation in the early phase (~2 hours) but enhanced inflammation in the late-phase (~48 hours) (29). COX-2 drives acute inflammation via recruiting leucocytes but promotes inflammatory resolution through mononuclear cells such as macrophages (29, 52). Importantly, COX-2 is required for thebiosynthesis of SPMs and resolution of inflammation (53, 54).

Many lines of evidence from different labs have demonstrated that SPMs are able to potently and effectively control inflammatory pain (31) (Table-1). Intraplantar (i.e., within the sole of the foot) injection of carrageenan induces signs of inflammation in rodents, such as neutrophil infiltration, edema, and upregulation of proinflammatory cytokines and chemokines (e.g., TNF, IL-1β, IL-6, and CCL2), as well as inflammatory pain (heat and mechanical hyperalgesia) for >24 hours. Intraplantar pretreatment of mice with very low doses of RvE1 or RvD1 (20 ng ~ 60 pmol) completely prevented inflammatory pain development and reduced the signatures of inflammation, including neutrophil infiltration, paw edema, and down-regulated the expression of pain-inducing IFMs (IL-1β, IL-6, TNF-α, and CCL2) (55).

Capsaicin and allyl isothiocyanate (AITC), known as mustard oil, are natural compounds and induce intense pain via activation of TRPV1 and TRPA1 receptors, respectively (5, 56) (Figure 1). Strikingly, capsaicin-induced spontaneous pain is blocked by RvE1 (55). Furthermore, capsaicin-induced pain is suppressed by MaR1, RvD2, NPD1 but not RvD1, whereas mustard oil-induced pain is inhibited by RvD1 and RvD2 but not RvE1, suggesting distinct modulation of inflammatory pain by SPMs (32, 57-59).

SPMs were shown to reduce different types of inflammatory pain (Table-1), including colitis or bacteria induced pelvic pain by RvD2 (1500 ng/rat, 300 ng/mouse, IP) (60), osteoarthritis-induced pain by intraperitoneal (IP) treatment of D series resolving precursor 17(R)-HDoHE (17(R)-HDHA, 300 ng/mouse) (61), and arthritis-induced joint stiffness by aspirin-triggered-RvD1 (AT-RvD1, 300 ng/rat, IP) (62, 63). Reduction of adjuvant-induced arthritic pain is much more efficacious by an RvD1 analogue (AT-RvD1, 1.5 mg/kg, 72 % pain inhibition) than opioid (morphine, 0.5 mg/kg, 34% pain inhibition), steroid (dexamethasone, 5 mg/kg, 12% pain inhibition), or COX-2 inhibitor (indomethacin, 5 mg/kg, 35% inhibition) (63). In a mouse model of rheumatoid arthritis, persistent arthritic pain is correlated with decreased levels of MaR1 but not with joint swelling. Systemic MaR1 administration caused sustained reversal of mechanical pain and reduced inflammatory macrophage infiltration in the DRG (64). Vulvodynia is an inflammatory condition and a common cause of pain in premenopausal women (65). In a murine vulvar pain model, topical treatment of MaR1 not only reduced PGE2 levels but also alleviated mechanical pain (65). MaR1 may also modulate trigeminal pain associated with the temporomandibular joint by modulation of inflammation-induced synaptic plasticity in the trigeminal nucleus (66). Lipoxins, such as lipoxin A4 (LXA4) and lipoxin B4 (LXA4), are biosynthesized from arachidonic acid and require lipoxygenases (e.g., LOX-5, LOX-12, and LOX-15) (67) (Figure 2). Intravenous (10 μg/kg) of LXA4 and LXB4 was found to inhibit carrageenan-induced inflammatory pain in rats (68).

The intrathecal route has been extensively used to deliver drugs to the spinal cord via an implanted catheter or direct lumbar puncture (69, 70). The intrathecal route can also deliver reagents (e.g., proteins, RNAs, DNAs) to the DRGs, which are partially covered by the meninges (14). Intrathecal injection of either RvE1 or RvD1 reduced adjuvant-induced heat and mechanical hypersensitivity within 10 min (62). These rapid effects of RvD1 and RvE1 suggest transcription-independent modifications by SPMs. Intrathecal pre-treatment of RvE1 (0.3 and 1 ng) also blocked the formalin-induced 2nd phase spontaneous pain through inhibition of central sensitization (55). Remarkably, the RvE1 dosage for inhibiting the formalin-induced 2nd phase pain is 100 times lower than that of morphine, highlighting the potency of SPMs (55). Intrathecal RvD2, NPD1, and MaR1 (1-10 ng) also alleviated persistent inflammatory pain following adjuvant injection without altering motor function in mice (58, 59). Interstitial cystitis syndrome is characterized by hyperalgesia and bladder overactivity. Intrathecal RvD2 not only reduced pelvic pain but also improved bladder function (71). Low-back pain is one of the most common chronic pain conditions. Intrathecal administration of MaR1 (10 or 100 ng) alleviated nucleus pulposus-induced mechanical and thermal hyperalgesia for several days and reduced the activation of NLRP3-mediated inflammasome in rats (72). In a rat model of lumbar disc herniation, intrathecal LXA4 reduced pain hypersensitivity, downregulated TNF-α and IL-1β expression, and upregulated TGF-β1 and IL-10 expression in the spinal cord (73).

Postoperative Pain

Postoperative pain is a main focus of anesthesiology research and was traditionally managed by opioids, which not only produce side effects but also delays recovery (74). In rodents, postoperative pain is induced by plantar incision, skin-muscle retraction, and bone fracture (75). While acute postoperative pain is mostly reminiscent of inflammatory pain, chronic postoperative pain after amputation and thoracotomy has characteristics of neuropathic pain (76). Prolonged muscle retraction produces postoperative pain for 3-4 weeks in humans and rodents (77). Intrathecal pre-treatment of RvE1 and RvD1 prevented the muscle incision-induced postoperative pain in rats (78). Intrathecal RvD1 and RvD2 also prevented or delayed the development of post-thoracotomy pain (79). Post-treatment of RvD1 at later time points is also effective, producing transient pain relief in the thoracotomy model (78). Tibial bone fracture induces postoperative pain for several weeks, intrathecal post-treatment of RvD1 and RvD5, but not RvD3 and RvD4, can alleviate postoperative pain including mechanical and cold hypersensitivity (46). Postoperative pain after bone fracture is also associated with cognitive decline, a comorbidity of chronic pain (80). Intriguingly, systemic treatment of AT-RvD1 in mice was able to prevent cognitive decline by control of neuroinflammation (81).

Neuropathic Pain

Neuropathic pain is induced by nerve injury, spinal cord injury, diabetes, and chemotherapy in animal models so as to resemble neuropathic pain in clinical settings (82). SPMs have demonstrated effectiveness in reducing neuropathic pain in animal models of those settings (83-86). Intrathecal administration of RvE1 and MaR1 reduced mechanical and thermal pain hypersensitivity after nerve injury by chronic constriction injury (CCI) of the sciatic nerve (83, 87). Peri-operative application of NPD1 (300 ng/mouse) on the sciatic nerve

around the ligatures prevented the development of mechanical allodynia. This pre-treatment also alleviated stump pain and autotomy, a self-mutilation behavior that occurs after nerve transection, an animal model of amputation (88). Mechanistically, RvE1 or NPD1 inhibited nerve trauma-induced glial activation and neuroinflammation in the mouse spinal cord (83, 88). Spinal NPD1 treatment also blocked long-term potentiation (LTP), a cellular mechanism of chronic pain (88, 89). Post-treatment of NPD1 via the intrathecal route, 2 weeks after nerve trauma, also inhibited mechanical allodynia, with an efficacy similar to gabapentin (a widely prescribed drug for the management of neuropathic pain), but with a potency 500 times higher than gabapentin (88). Repeated injections of NPD1 produced no side effects or signs of analgesic tolerance (88), whereas gabapentin is known to impair cognition. After spinal nerve ligation, intrathecal MaR1 administration inhibited neuropathic pain and neuroinflammation in rats, as evidenced by the downregulation of NF-κB p65 nuclear translocation and protein levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6). Moreover, this treatment maintained synaptic integrity by restoring the expression of synaptic proteins (PSD95 and synapsin II) in rat spinal cord with nerve injury (90). In a mouse model of diabetic neuropathy, intrathecal NPD1 also relieved streptozotocin-induced mechanical allodynia (85). Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of chemotherapy drugs, such as paclitaxel (91, 92). In mice, intrathecal post-treatment of RvD1, RvD2, and RvD5, but not RvD3 and RvD4, alleviated chemotherapy-induced neuropathic pain (84). 3-oxa-$PD1_{n-3}$DPA is a novel analogue of PD1/NPD1 (85). Intrathecal administration of 3-oxa-$PD1_{n-3}$ DPA, PD1, or $PD1_{n-3}$ DPA (30-100 ng) each significantly relieved streptozotocin-induced neuropathic pain (mechanical allodynia) in mice. However, at a low dose (10 ng), only 3-oxa $PD1_{n-3}$ DPA was able to alleviate diabetic neuropathic pain, due to increased metabolic stability of 3-oxa-$PD1_{n-3}$ DPA when compared to PD1 and $PD1_{n-3}$ DPA (85). Spinal cord injury (SCI) results in central neuropathic pain, which is driven by glial activation and neuroinflammation (93). Intrathecal LXA4 treatment (300 pmol) at 4 and 24 hours after spinal cord hemisection produced marked reductions in SCI-induced mechanical pain, microgliosis, and pro-inflammatory cytokines (86). In primary culture of microglia, LXA4 inhibited TNF-α release through microglial ALX/FPR2 receptors (86).

Cancer Pain

Cancer pain produced by bone cancer is often severe and difficult to treat (94). In a mouse model of bone cancer produced by implantation of osteolytic fibrosarcoma, RvD1 and RvE1 exhibited antinociceptive potencies in reducing heat and mechanical pain following intrathecal administration (95). Interestingly, RvD1 increased levels of the endocannabinoids anandamide and 2-Arachidonoylglycerol in the spinal cord, suggesting a connection between SPM and endocannabinoid signaling (95). In mouse models of oral squamous cell carcinoma, daily IP injections of 200 ng RvD2 decreased tongue tumor size. (96). This treatment also attenuated cancer-induced thermal, mechanical, and spontaneous pain in mice (96).

Furthermore, resolution failure may cause carcinogenesis (97). Thus, resolvins have been shown to suppress tumor growth and enhance cancer therapy (44). Traditional cancer therapies, such as chemotherapy and radiotherapy, reduce tumor burden by killing tumor

cells. Notably, tumor cell debris can trigger inflammation to promote tumor growth. SPMs, such as RvD2, RvD2, and RvE1 each markedly reduced debris-stimulated tumors. Mechanistically, SPMs stimulate macrophage phagocytosis in local tumor environment and inhibit the release of inflammatory cytokines and chemokines, such as TNFα, IL-6, IL-8, CCL4, and CCL5. SPM-mediated endogenous clearance of tumor cell debris through macrophage phagocytosis may offer a new therapeutic strategy (44). In a mouse model of lung cancer, induced by inoculation of Lewis lung carcinoma (LLC) cells, aspirin-triggered SPMs, such as AT-RvD1, AT-RvD3, and AT-LXA4 (600 ng/kg/day) inhibited primary tumor growth through macrophage phagocytosis of therapy-generated tumor cell debris (98). Metastasis of cancer to the bone cavity produces bone destruction and severe bone cancer pain (99, 100). Immunotherapies such as monoclonal antibodies against PD-1 (program death protein 1) and agonists of STING (stimulator of interferon gene) were able to alleviate bone cancer pain through inhibition of osteoclast formation and prevention of bone destruction (99, 100). Thus, it is of great interest to investigate the role of SPMs in bone destruction in cancer pain.

Physiological Pain

Physiological pain is important for the maintenance of homeostasis in the nervous system and immune system (2). Analgesics such as opioids and local anesthetics suppress physiological pain, making animals and humans insensitive to pain. Suppression of physiological pain can be detrimental and even lethal, in the case of heart attacks without pain or congenital insensitivity to pain in individuals with mutations in SCN9A, which encodes the sodium channel subtype Nav1.7 (101). Importantly, SPMs do not interfere with normal pain perception: local or systemic injection of resolvins has no effects on thermal or mechanical pain sensitivity in rats and mice under steady-state conditions (58, 62). NPD1 and RvD2 do not change basal synaptic transmission in the spinal cord pain circuit in physiological conditions, although they potentially abolish inflammation-induced synaptic plasticity (58, 59). Other studies confirmed that RvD1 and RvE1 show no effects on acute nociception or motor function in naïve mice (95). Thus, SPMs serve to restore the homeostatic balance of pain without suppressing physiological pain. Similarly, in the immune system SPMs control excessive inflammation but are not immune suppressants (53).

Distinct Analgesic Potency of DHA and DHA-derived SPMs

Numerous DHA-derived SPMs have been identified, including RvD1-RvD6, NPD1, MaR1, MaR2, etc. Notably, SPMs and their precursor DHA exhibit distinct analgesic properties. DHA appears to be effective in pain relief following pre-treatment at much higher doses (100-1000 fold of that of SPMs), presumably via the DHA receptor GRP120 (102), whereas SPMs show efficacy and potency in both pre- and post-treatment (46). Pre-treatment with DHA reduces neuropathic and postoperative pain (46, 88). In contrast, intrathecal DHA post-treatment does not reduce neuropathic pain after nerve injury or post-operative pain after bone fracture, even at high doses (500 μg, 1000-fold of SPMs) (46, 88). Thus, giving more SPM precursor (e.g., DHA) cannot substitute for the efficacy of SPMs in chronic disease conditions, because DHA cannot be effectively converted to SPMs, most likely due to disruption of SPM biosynthesis.

Sex Differences in SPM Regulation of Pain

The majority of preclinical studies in pain research, including SPM-related studies, are conducted in male animals, even though females have a higher incidence of chronic pain such as migraine and fibromyalgia (103, 104). Recent studies have also shown sex dimorphism in microglia and macrophage regulations of pain (12, 105). Intriguingly, intrathecal RvD5 inhibited inflammatory and neuropathic pain in male mice but not in female mice. In contrast, intrathecal RvD1, RvD2, NPD1, MaR1 reduced chemotherapy-induced mechanical allodynia in both sexes (84). Based on the sex dimorphism of microglial and macrophage signaling in pain (12, 105), intrathecal RvD5 may act on microglia and/or macrophages to mediate male-specific pain relief. Future studies that investigate the role of sex hormones in regulating the production and analgesic actions of SPMs may thus be of interest.

SPMS CONTROL PAIN VIA GPCR SIGNALING AND NEUROIMMUNE MODULATION

SPMs exert their actions by activating G protein-coupled receptors (GPCRs)(106). Multiple SPM receptors have been identified: including ChemR23 (ERV1) for RvE1 and RvE2, GPR32 (DRV1) for RvD1 and RvD5, and GPR18 (DRV2) for RvD2 (107-109). SPM receptors are expressed by macrophages, neutrophils, nociceptive sensory neurons and glial cells (Figure 3, Figure 4). Spinal astrocytes and microglia express ALX (FPR2) to mediate the analgesic effects of LXA4 (68, 86). RNAseq analysis reveals that microglia express ChemR23, GPR32, and GPR18 (106, 110).

RvE1/ChemR23 Axis in Pain Resolution

Arita et al. screened receptors for RvE1 and identified ChemR23 (ERV-1, CMKLR1) and confirmed specific binding of this receptor to RvE1 using [^{3}H]-labeled RvE1. ChemR23 is required to mediate RvE1's regulation of NF-κB signaling and IL-12 expression in dendritic cells (111). Further studies revealed that RvE1 also binds leukotriene B4 receptor BLT1 in polymorphonuclear leukocytes and serves as a local inhibitor of BLT2 signaling on leukocytes (112). ChemR23 is expressed at high levels in monocytes, but at lower levels in neutrophils and T lymphocytes (111). Xu et al. demonstrated that RvE1's analgesic actions were mediated by ChemR23, as knockdown of ChemR23 expression in the DRG and spinal cord by intrathecal injection of specific siRNA was sufficient to block RvE1-induced antinociception in mice. Furthermore, chemerin, a natural peptide ligand for ChemR23 could produce similar analgesic effect as RvE1 (55). Endogenous chemerin and ChemR23 also contribute to the resolution of inflammatory pain (113). Microglia express ChemR23 (106, 114), and RvE1 inhibits TNF-α production and release in spinal microglial cultures (83). Chronic arthritis is associated with down-regulation of *Chemr23* mRNA levels in rat osteoarthritis (OA) joint tissue (61). Moreover, systemic treatment of 17(R)-HDHA) not only reversed arthritic pain but also increased ChemR23 expression in the spinal cord (61). Due to the short half-lives of RvE1 and chemerin, a 9-amino acid-tethered chemerin fragment was developed as a stable chemerin analog. This membrane-anchored ChemR23

agonist reduced neuropathic pain for more than 24 hours after a single intrathecal injection (115). Together, these findings support an active role of ChemR23 in the resolution of pain.

NPD1/GPR37 Axis in Pain Resolution

Recently, Bang et al. demonstrated several lines of evidence that NPD1 acts on macrophage-expressing GPR37 for the resolution of inflammatory pain and infection-induced pain (33, 34). First, NPD1 activation of GPR37 induced macrophage phagocytosis of zymosan particles via increasing intracellular Ca^{2+} and activation of ERK signaling (33). NPD1 also triggered GPR37-dependent phagocytosis of listeria bacteria by macrophages (34). Second, intraplantar injection of zymosan, which can activate TLR2, elicited inflammatory pain that normally resolves in several days. However, mice lacking *Gpr37* failed to resolve this inflammatory pain (33). Intraplantar injection of listeria elicited severe inflammatory pain that normally resolves in 2 weeks but this resolution process is disrupted in *Gpr37* knockout mice (34). Third, depletion of macrophages impaired the resolution of zymosan-induced inflammatory pain (33), whereas adoptive transfer of wild-type macrophages, treated with GPR37 agonist, was sufficient to reverse listeria-induced inflammatory pain (34). Additionally, GPR37 regulates the macrophage phenotype: a lack of GPR37 results in a switch from a M2-like to M1-like macrophages, which have an upregulation of pro-inflammatory cytokines (IL-1β, IL-β, IL-6) and the downregulation of anti-inflammatory cytokines (IL-10, TGF-β1) (33, 34, 116). Single-cell RNA sequencing has revealed GPR37 expression in DRG neurons of rodents and non-human primates (117, 118), but this expression is downregulated in mouse DRG neurons after nerve injury (117). Thus, loss of GPR37 in both macrophages and sensory neurons may contribute to the pathogenesis of chronic pain.

Receptor Signaling for RvD2 and MaR1

Specific binding of RvD2 to recombinant GPR18 was confirmed using a ^{3}H-labeled-RvD2. RvD2 limited PMN infiltration and enhanced phagocyte clearance of bacteria, but these effects are lost in *Gpr18*-deficient mice (108). Interestingly, oral cancer pain is correlated with the downregulation of mRNA levels for *Gpr18* and *Gpr32* in cancer tissue (96). DRG nociceptive neurons express GPR18, but bladder inflammation resulted in a marked reduction of GPR18 in DRG neurons. Functionally, the GPR18 antagonist O-1918 blocked the therapeutic effects of RvD2 (71). Leucine-rich repeat containing G-protein-coupled receptor 6 (LGR6) is a marker of osteoprogenitor cells and is dynamically expressed during the differentiation of bone in mouse and human mesenchymal stem cells. Recently, LGR6 was identified as a MaR1 receptor, its actions were significantly amplified with LGR6 overexpression but diminished by Lrg6 gene silencing in phagocytes (119). MaR1 stimulates LGR6-mediated cAMP activity during osteogenesis (120). Additionally, MaR1 was shown to activate orphan nuclear receptor RORα (retinoic acid-related orphan receptor α) to regulate M1/M2 polarization in hepatic residential Kupffer cells and control the pathogenesis of nonalcoholic steatohepatitis (NASH) (121).

Regulation of TRP Channels and Synaptic Plasticity by SPMs

SPMs are potent inhibitors of TRPA1 and TRPV1 and have distinct effects on TRPA1- and TRPV1 -mediated pain (32, 55, 57, 58, 122). Consistent with those observations, SPMs

also differentially inhibit the function of TRPA1 and TRPV1 in cultured DRG neurons (57-59). Interestingly, RvD2 potently inhibits the function of both TRPV1 (IC_{50} = 0.1 nM) and TRPA1 (IC_{50} = 2 nM) in mouse DRG neurons. (58). MaR1 also potently inhibited TRPV1 function in trigeminal sensory neurons collected from animals with inflammatory pain in the temporomandibular joint (66). Bladder inflammation resulted in upregulation of TRPV1 and RvD2 receptor GPR18 in the same DRG neurons, and RvD2 inhibited capsaicin-induced calcium influx in DRG neurons from bladder-inflamed rats. This effect of RvD2 was blocked by the GPR18 antagonist O-1918, supporting the involvement of GPR18 in regulating the RvD2's inhibition of TRPV1 (71). RvD2 also reduced the capsaicin-induced Ca2+ response of rectal submucosal neurons from patients with inflammatory bowel syndrome, suggesting the clinical relevance of the RvD2/TRPV1 axis (60). PSB-KK-1415, an agonist of GPR18, has anti-inflammatory and anti-nociceptive activities in animal models of intestinal inflammation and inflammatory pain (123). Additionally, RvD3 inhibited TRPV1 signaling in mouse and human DRG neurons (124). It is generally believed that SPMs inhibit TRP channel via Gi-mediated GPCR signaling in sensory neurons (59, 60, 66), but SPMs at high concentrations may also alter TRP channel activity via lipid raft modification at the cell membrane (125). Interestingly, long-term potentiation (LTP), a cellular mechanism of learning and memory identified in hippocampal neurons, was found in the pain circuit and contributes to persistent pain (126). Spinal cord administration of NPD1 and RvD1 was able to reverse C-fiber stimulation-evoked spinal cord LTP in intact animals (59, 89). Spinal treatment with NPD1 blocked TNF-induced synaptic plasticity and pain hypersensitivity (59). Thus, apart from immune/glial modulation, SPMs control pain via neuromodulation in the PNS and CNS (Figure 4).

SPMs CONTROL ACUTE AND CHRONIC ITCH

Although pain and itch are highly related, itch (pruritus) is a distinct sensation, triggering scratching responses following activation of pruriceptors in primary sensory neurons, which are a subset of nociceptors (127). Acute itch is typically defined as histamine-dependent itch, induced by histamine and compound 48/80, and histamine-independent itch, induced by chloroquine (127). Notably, TRPV1 and TRPA1 are also expressed by pruriceptors (Figure 1) and play distinct roles in regulating histamine-dependent and histamine-independent itch. While pain is known to suppress itch, scratching-induced skin injury may exacerbate itch. Chronic itch involves skin injury and dermatitis. SPMs have been shown to alleviate itch by reducing skin inflammation. Eczema is commonly associated with persistent pruritus. In a double-blinded, placebo-controlled, randomized study with 60 patients, topic treatment of LXA4 cream significantly relieved the severity of infantile eczema and improved the quality of life, however, pruritus was not directly quantified in this study (128). LXA4 controlled skin inflammation in an animal model of psoriasis by downregulating TLR4 signaling (129). RvE1 attenuates murine psoriatic dermatitis by inhibiting migration of cutaneous dendritic cells and γδ T cells (130). Systemic RvD3 treatment prevented the development of psoriasiform itch and skin inflammation. Mechanistically, RvD3 was shown to inhibit TRPV1 signaling in mouse and human DRG neurons, which may account for the acute anti-itch effects of RvD3 (124). Cutaneous T-cell lymphoma (CTCL) is associated with chronic itch in patients and animals (131). Intrathecal

administration of PD-1, PD1n-3 DPA, and the new analog 3-oxa-PD1n-3 DPA significantly reduced scratching for several hours (85). Taken together, SPMs may alleviate chronic itch via effective control of skin inflammation and inhibit acute pruritus via regulation of TRP channel function (Figures 1, 2, 4). A recent study suggests that spinal glial cells play an important role in driving chronic itch (80). It will thus be of interest to investigate how SPMs regulate glial activation and neuroinflammation in chronic itch.

MRGPR receptors are a family of mas-related GPCRs and MrgprA3 has been identified as an itch receptor in mice (132). Recently, the structures of MRGPRX2 and MRGPRX4 (the proposed human itch receptors) were solved (133, 134), which should accelerate the structure-guided discovery of therapeutic agents for pain and itch. Although the structures of SPM receptors remain to be solved, it is of great interest to investigate possible interactions between SPM receptors and MRGPRs.

CONCLUSIONS AND FUTURE DIRECTIONS

The resolution phase of inflammation and pain is now widely recognized as an active biological process, governed by a superfamily of endogenous chemical mediators that stimulate resolution of inflammatory responses, namely SPMs (41). As a natural response for the resolution of inflammation and pain, SPMs have gained great attention in the past decade as a newly recognized class of pain killers (31). Many laboratories worldwide have confirmed potent analgesic actions of SPMs in various animal models (Table 1). However, no SPM-related treatment has been as-yet approved by the FDA. SPMs are derived from omega-3 PUFAs, which have shown benefits in humans with various pain-related conditions, such as chronic headaches, migraines, joint discomfort, sickle cell disease, diabetic neuropathy, and rheumatic diseases (135, 136). In December 2019, FDA approved Vascepa (Icosapent Ethyl, an omega-3 fish oil medication that contains EPA) for reduction of the risk for heart attack and stroke. In a randomized trial, Ramsdon and collaborators have shown that dietary omega-3 fatty acids may alleviate headache by producing SPM precursors (136, 137). Notably, SPMs have wide safety profile, and so far no neurotoxicity or cellular toxicity of SPMs has been reported. Since SPMs are produced naturally in humans, SPM-containing softgels are sold in the marker as nutritional and dietary supplement.

SPMs have been tested in several human trials. An early clinical trial on infantile eczema (a condition associated with itch) demonstrated the first successful treatment of the disease with a topical LXA4 analog (128). Methyl ester-benzo-lipoxin A4 (BLXA4), an oral rinse containing a LXA4 mimetic, is well tolerated by patients, and once-daily rinsing with BLXA4 for 28-days decreased gingival inflammation and increased serum levels of SPMs (138). Additionally, RX-10045, a derivative of RvE1 in topical eye drops, has progressed to clinical trials to evaluate ocular inflammation and pain in patients with cataract surgery (NCT02329743).

A major limitation of SPMs is that they are metabolically unstable and can be rapidly inactivated *in vivo*. It is noteworthy that 19-pf-RvE1, a metabolically stable form of RvE1 (139), extended the anti-hyperalgesic effect of RvE1 from two hours to 6 hours (55). The

pro-resolving effects of AT-RvD1 was also prolonged by constructing RvD1-containing nanoparticles (140). Furthermore, 3-oxa PD1n-3 DPA, a novel analogue of PD1/NPD1, displays increased metabolic stability (compared to other PD1 analogues) and greater analgesic efficacy at a low dose (93). Hence, improving the PK of SPMs, using different analogs or unique delivery system (e.g., degradable polymeric vehicle) (141), could prolong and enhance the analgesic and pro-resolving benefits of SPMs. Although high doses of Omega-3 PUFA may bolster the biosynthesis of SPMs, this normal biosynthetic process can be disrupted by diseases. Our body's ability to produce SPMs may be compromised in clinical settings of chronic pain that is associated with arthritis, diabetes, obesity, and aging. However, SPMs are still produced in many disease conditions (41), which may contribute to the resolution of chronic diseases in some patients.

An alternative approach is to boost endogenous production of SPMs by neuromodulation. For example, vagus nerve stimulation (VNS) can powerfully regulate inflammation and neuroinflammation, in part via increasing the SPM production (142, 143) (Figure 2). Conversely, vagotomy reduced local production of SPMs (144). Human vagus produces SPM and VNS increased SPMs, meanwhile decreasing pro-inflammatory prostaglandins and leukotrienes (142, 145). Auricular VNS via electroacupuncture significantly increased RvD1 level in DRGs of animals with chemotherapy (142). Furthermore, spinal cord stimulation, an effective clinical treatment for chronic pain, significantly increased the level of RvD1 in the cerebrospinal fluid (146). Studying the synergistic actions between a healthy diet containing Omaga-3 PUFA and neuromodulation may prove useful for the prevention and reversal of pain through regulation of inflammation and neuroinflammation (143).

Lastly, it is of great importance to investigate how endogenous SPM signaling regulates the homeostasis, initiation, chronification (a pain that can last more than 3 months), and resolution of pain. Several receptors of SPMs have been identified and knockout mice lacking these SPM receptors can be utilized to study their functions. It is worth characterizing the host receptors and their signaling pathways that mediate the biological functions of different SPMs in immune cells, glial cells, and neurons. Given the ongoing opioid epidemic in the United States, there is an urgent need to develop non-opioid analgesics (147). The combination of analgesic, anti-inflammatory, and pro-resolving properties of SPMs, as a resolution pharmacology (148), offers a great potential for the control of acute and chronic pain and itch. SPMs have also demonstrated efficacy in other inflammatory conditions, such as allergy, colitis, lung injury, peritonitis, bacterial infection, and Alzheimer's disease (31, 41, 149) (Table 1). Thus, the scope of the SPM-based resolution pharmacology is beyond pain and itch control and should cover many inflammation-related diseases.

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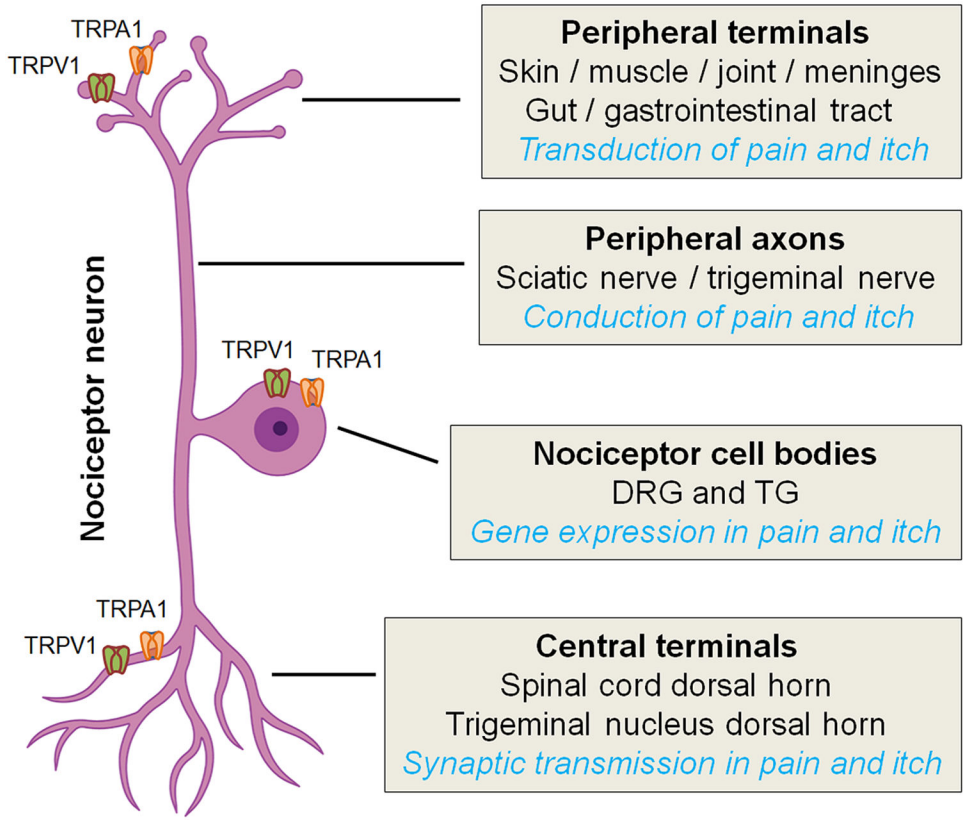

Figure 1.

Schematic of nociceptor neurons and their functions. Nociceptor cell bodies reside in dorsal root ganglia (DRG) and trigeminal ganglia (TG). Nociceptor neurons have two axons: peripheral axons terminate in the skin, muscle, and gut and central axons terminate in the spinal cord and trigeminal nucleus dorsal horn. A subset of nociceptor neurons can also sense itch as pruriceptors. TRPV1 and TRPA1 ion channels are critical for the transduction and transmission of both pain and itch.

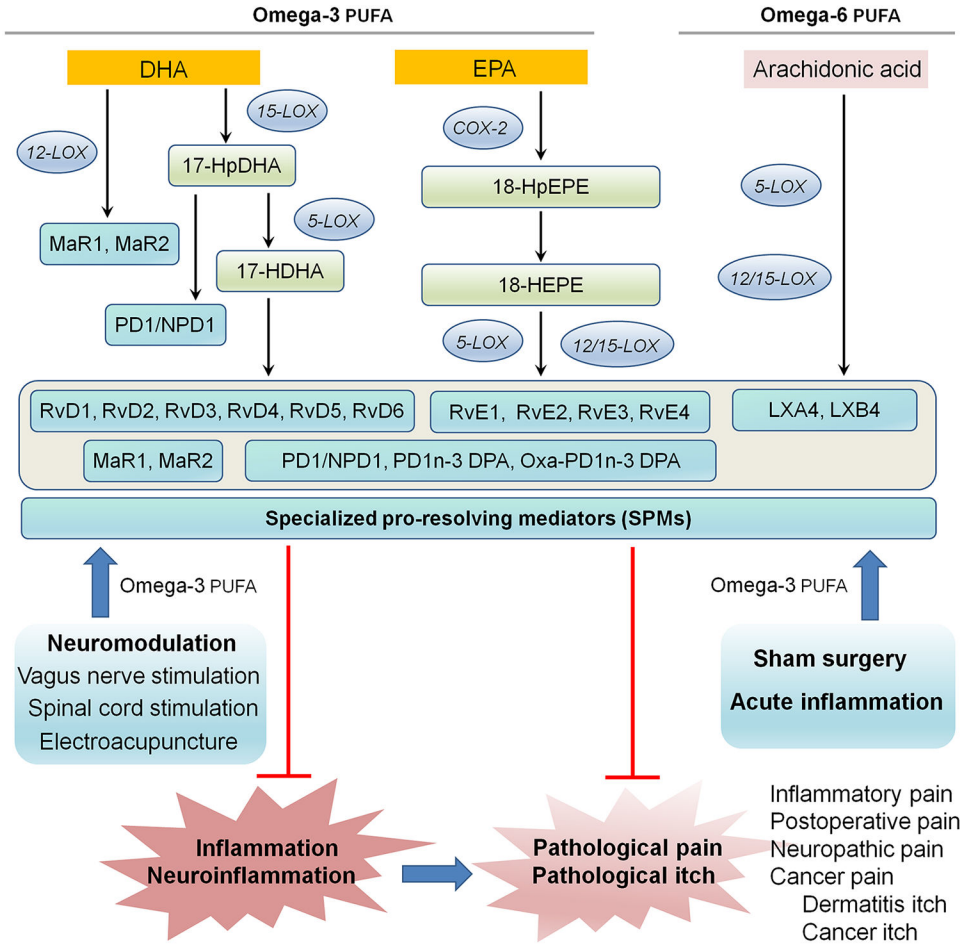

Figure 2.

Schematic of SPM biosynthesis and the actions of SPMs in the control of inflammation, neuroinflammation, pathological pain and itch. SPMs (resolvins, protectins, maresins, and lipoxins) are primarily biosynthesized from omega-3 poly-unsaturated fatty acids (Omega-3 PUFA, including EPA and DHA) and Omega-6 PUFA (arachidonic acid) via different lipoxygenase (LOX) and cyclooxygenase (COX) enzymes. SPM production is facilitated by neuromodulation, such as vagus nerve stimulation, spinal cord stimulation, and electroacupuncture, sham surgery, and acute inflammation.

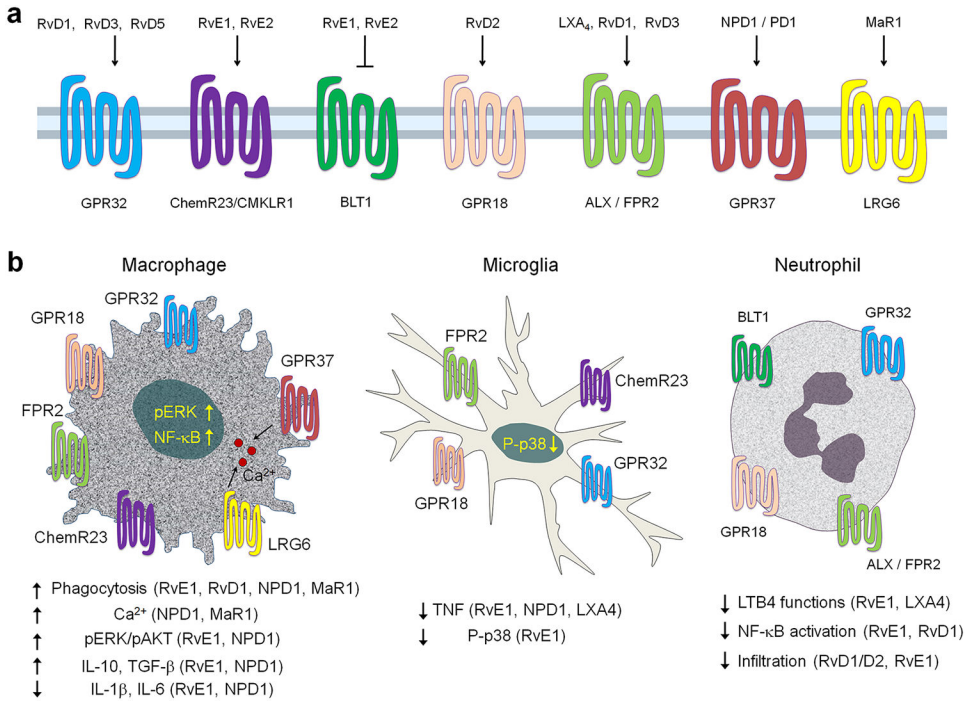

Figure 3.

SPM receptors and SPM actions on macrophages, microglia, and neutrophils. (a) SPMs receptors for resolvins, protectins, maresins, and lipoxins. SPMs signal through GPCRs and multiple SPMs share the same receptors. (b) SPMs activate their respective receptors (GPCRs) to regulate the function of macrophages, microglia, and neutrophils and produce anti-inflammatory and pre-resolving effects. Abbreviation: ERK, extracellular signal-regulated kinase.

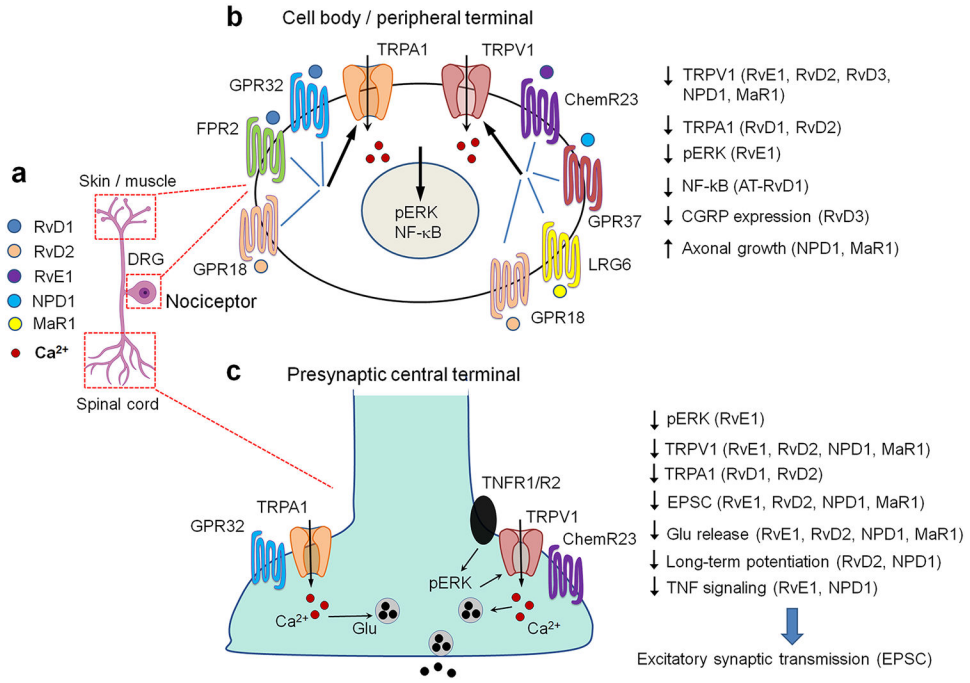

Figure 4.

SPMs act on nociceptive sensory neurons to regulate ion channel function, synaptic transmission, and axonal growth. (a) Location of nociceptor cell body in DRG, peripheral axons terminals in skin and muscle, and central axonal terminals in the spinal cord. (b) SPM receptor signaling in nociceptor cell body and peripheral terminal, leading to reduced activity of TRPV1 and TRPA1 and increased axonal growth. (c) SPM receptor signaling in nociceptor central terminal, leading to reductions in TRPV1 and TRPA1 activity, glutamate release, excitatory synaptic transmission, and spinal cord pain transmission. Abbreviations: EPSC, excitatory postsynaptic current, ERK, extracellular signal-regulated kinase, Glu, glutamate.

Table-1.

Beneficial effects of synthetic SPMs in the control of pain, itch, and inflammatory diseases. SPMs reduce pathological pain and itch in animal disease models and human diseases. SPMs also control disease progression in other inflammatory disorders in animal models. Abbreviations: IT, intrathecal, IP, intraperitoneal, IPL, intraplantar, IV, intravenous.

Pain/itch models	SPMs	Species/Route	Effects	References
Inflammatory pain				
Capsaicin {TRPV1)	RvE1, RvD2/D3, MaR1, NPD1	mice, IPL	Spontaneous pain ↓	55, 58, 59
Mustard oil (TPA1)	RvD1, RvD2	mice, IPL	Spontaneous pain ↓	57, 58,
Formalin	RvE1, NPD1, RvD5	mice, IT	Spontaneous pain ↓	55, 59, 84
Carrageenan	RvD1, RvE1, LXA4, LXB4	mice/rats IT, IV	Heat and mechanical pain ↓	55, 68
CFA	RvD1, RvD2, RvE1, NPD1	mice, IT	Heat hyperalgesia ↓	55, 58, 59
Visceral pain	RvD2	mice, rats, IP	Visceral pain ↓	60
Bladder pain	RvD2	rats, IT	Mechanical pain ↓	71
Low back pain	LXA4, MaR1	rats, IT	Mechanical pain ↓	72, 73
Vulvodynia	MaR1	mice, topical	Mechanical pain ↓	65
Osteoarthris	17{R)-HDHA, AT-RvD1	rats / IP	Spontaneous & mechanical pain ↓	41, 61
Rheumatoid arthritis	MaR1, AT-RvD1	mice/rats, IP	Mechanical pain ↓	63, 64
Neuropathic pain				
Nerve injury (CCI)	RvE1, MaR1, NPD1	mice, IT	Mechanical and heat pain ↓	83, 87. 88
Spinal cord injury	LXA4	mice, IT	Mechanical allodynia ↓	86
Chemotherapy	RvD1, RvD2, MaR1	mice, IT	Mechanical allodynia ↓	84
Diabetic neuropathy	3-oxa-PD1n-3 DPA	mice, IT	Mechanical allodynia ↓	85
Post-operative pain				
Muscle retraction	RvD1, RvE1	rats, IT	Mechanical allodynia ↓	78
Thoracotomy	RvD1, RvD2	rats, IT	Mechanical and nocifensive pain ↓	79
Tibial bone fracture	RvD1, RvD2, MaR1	mice, IV, IT	Mechanical pain ↓	46
Cancer pain				
Oral cancer pain	RvD2	mice, IP,	Mechanical $ spontaneous pain ↓	96
Bone cancer pain	RvD1, RvE1	mice, IT	Mechanical and thermal pain ↓	95
Dermatitis and itch				
Eczema	LXA4	human, topic	Infantile eczema severely ↓	128
Psoriasiform itch	RvD3	mice, topic	scratching ↓	124
Cancer itch	3-oxa-PD1n-3 DPA	mice, IT	scratching ↓	85

Inflammatory diseases	SPMs	Species/Route	Effects	References
Allergy	RvE1, RvD1	mice, IP	Decreased allergic airway inflammation	31
Colitis	RvE1, RvD5	mice, IP	Reduced neutrophil recruitment & increased survival	31, 41
Lung injury	RvE1	mice, IP	Inhibited acute lung injury & bacterial pneumonia	31, 41
Peritonitis	RvD1/D2	mice, IP	Reduced neutrophil recruitment & alveolar bone loss	31, 41
Infection/sepsis	RvD2, NPD1, MaR1	mice, IP	Inhibited sepsis and increased survival	31, 34, 41
Kidney injury	RvD1	mice, IP	Increased Treg cells & alleviated renal tubular injury	31, 41
Alzheimer's disease	RvE1, LXA4	mice, IP	Inhibited glial activation and neuroinflammation	41, 146