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Pharmacology of inflammatory pain: local alteration in receptors and mediators

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Abstract

Background—Inflammation is commonly associated with hyperalgesia. Ideally, this change should abate once inflammation is resolved but this is not necessarily the case because phenotypic changes in the tissue can persist, as appears to be the case in postinfectious irritable bowel syndrome. Basically, all primary afferent neurons supplying the gut can sensitize in response to proinflammatory mediators, and the mechanisms whereby hypersensitivity is initiated and maintained are thus of prime therapeutic interest.

Experimental and clinical findings—There is a multitude of molecular nocisensors that can be responsible for the hypersensitivity of afferent neurons. These entities include: (i) receptors and sensors at the peripheral terminals of afferent neurons that are relevant to stimulus transduction, (ii) ion channels that govern the excitability and conduction properties of afferent neurons, and (iii) transmitters and transmitter receptors that mediate communication between primary afferents and second-order neurons in the spinal cord and brainstem. Persistent increases in the sensory gain may result from changes in the expression of transmitters, receptors and ion channels, changes in the subunit composition and biophysical properties of receptors and ion channels or changes in the structure, connectivity and survival of afferent neurons. Particular therapeutic potential is attributed to targets that are selectively expressed by afferent neurons and whose number and function are altered in abdominal hypersensitivity.

Conclusion—Emerging targets of therapeutic relevance include distinct members of the transient receptor potential (TRP) channel family (TRPV1, TRPV4, TRPA1), acid-sensing ion channels, protease-activated receptors, corticotropin-releasing factor receptors and sensory neuron-specific sodium channels.

Keywords

primary afferent neurons; inflammatory pain; hypersensitivity; hyperalgesia; upregulation of receptors; nocisensors; TRPV1; neuropeptides

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Introduction

Abdominal pain, especially gastrointestinal (GI) hyperalgesia, is poorly understood. This is in particular true for functional GI disorders such as irritable bowel syndrome (IBS). Although there is emerging evidence that IBS and inflammatory bowel disease may represent different points on a continuum between inflammatory and functional GI diseases [1-4], the inflammation and immune activation associated with IBS is too low to be seen in routine diagnosis. GI hyperalgesia thus differs from somatic hyperalgesia, which is a common comorbidity of tissue injury and inflammation [5]. Since infectious gastroenteritis is a major risk factor for the delayed development of IBS [1-3,6], it is appropriate to hypothesize that the inflammation triggered b acute infection is causally related to the later development of IBS. It appears as if the inflammatory response induces a change in the nociceptive system that persists despite the fact that the inflammation has largely, but not completely, abated. Ideally, hyperalgesia should go away once inflammation is resolved, and a major question is why this is not necessarily the case. In an appreciable proportion of patients IBS appears to be associated with intestinal inflammation in remission [6]. It would seem, therefore, that phenotypic changes in the nociceptive system persist not only in chronic inflammation but, as emerging evidence suggests, are also maintained to a certain degree in postinfectious IBS.

Basically, all primary afferent neurons supplying the gut can sensitize in response to proinflammatory mediators [5,7], and the mechanisms whereby hypersensitivity is initiated and maintained are thus of prime therapeutic interest. The present article focuses on select mechanisms that underlie the sensitization of GI afferent neurons under conditions of inflammation and concentrates on emerging drug targets that may provide new options in the treatment of GI pain and hyperalgesia. Progress in this area is badly needed in view of the prevalence of chronic visceral pain syndromes and their socio-economic burden [8]. The current treatment of visceral pain is unsatisfactory because the availability of visceral analgesics is limited, given that the utility of nonsteroidal anti-inflammatory drugs and opioid analgesics, which are the mainstay in somatic pain management, is restricted by their severe adverse effects on GI mucosal homeostasis and motility, respectively.

Inflammatory pain and hyperalgesia

It is well established that a variety of proinflammatory mediators including prostanoids, neurotrophic factors, ligands of protease-activated receptors, bradykinin, acidosis, 5-hydroxytryptamine (5-HT) and cytokines sensitize the peripheral fibres of primary afferent neurons subserving pain [7-9]. Peripheral sensitization represents a form of stimulus-evoked nociceptor plasticity in which prolonged stimulation in the context of injury or inflammation leads to a change in the chemical milieu that permits nociceptor firing at lower thresholds than that required for an acute noxious stimulus [7]. As a result, the pain threshold at the site of injury or inflammation is lowered and primary hyperalgesia ensues.

As long as it is reversible, sensitization of nociceptors results from modulation of nerve fibre excitability via post-translational changes such as phosphorylation of receptors, ion channels or associated regulatory proteins [9]. In contrast, enduring increases in the sensory gain are

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related to changes in the expression of transmitters, receptors and ion channels, changes in the subunit composition and biophysical properties of receptors and ion channels, or changes in the phenotype, structure, connectivity and survival of afferent neurons [8,9].

Sensory neurons as targets in the control of gastrointestinal hyperalgesia

Although it is emerging that many relays in the gut–brain axis are perturbed in visceral pain, sensory neurons stage as the first element at which to aim novel therapies. In addition, drugs that target nociceptive afferent neurons can be configured such as not to enter the brain and hence being free of adverse effects on central functions. Sensory neuron-selective targets can be grouped into (i) receptors and sensors at the peripheral terminals of afferent neurons that are relevant to stimulus transduction, (ii) ion channels that govern the excitability and conduction properties of afferent neurons and control transmitter release, and (iii) transmitters and transmitter receptors that mediate ascending and descending transmission in the central synapses of primary afferent neurons in the spinal cord and brainstem (Table 1). However, sensory neuron-targeting drugs can also have disadvantages inasmuch as they may interfere with important physiological functions of primary afferents and with the regulatory roles of peripheral neurons of the enteric and autonomic nervous system. Furthermore, they will be ineffective if hyperalgesia is solely the result of central sensitization processes.

Drug targets on visceral sensory neurons

Serotonin (5-HT) receptors

Most of the 5-HT present in the body is formed in GI enterochromaffin cells. 5-HT released from these cells targets 5-HT_3 receptors on vagal afferent neurons to cause nausea and vomiting. A single nucleotide polymorphism of the serotonin reuptake transporter (SERT) is associated with IBS, a feature that reduces SERT function and thus enhances the availability of 5-HT at 5-HT receptors [10]. In addition, inflammatory cytokines can also inhibit SERT [11]. Experimental and clinical studies attest to an implication of 5-HT_3 receptors in IBS-associated pain. However, the utility of the 5-HT_3 receptor antagonist alosetron licensed for the treatment of diarrhoea-predominant IBS in female patients is limited by its propensity to cause constipation and increase the risk of ischaemic colitis. The partial 5-HT_4 receptor agonist tegaserod is also able to reduce pain in IBS, but marketing of this drug has been suspended because of a risk of adverse cardiovascular events.

Cholecystokinin CCK_1 receptors

Cholecystokinin (CCK) can excite vagal afferents via activation of CCK_1 receptors. Clinical observations attribute CCK a role in functional GI disorders, but trials involving CCK_1 receptor antagonists such as dexloxiglumide have not yet proved the therapeutic utility of this concept [12].

Somatostatin receptors

An implication of somatostatin in abdominal pain has been deduced from the ability of octreotide, a long-acting analogue of somatostatin, to reduce the perception of gastric and

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rectal distension and to increase discomfort thresholds in IBS patients, but not healthy controls [13]. This antinociceptive effect may be peripheral, given that somatostatin SST_2 receptor activation by octreotide inhibits chemo- and mechanosensitive spinal afferents innervating the rat jejunum [8].

Prostanoid receptors

Inflammation induces cyclooxygenase-2 to synthesize large quantities of prostaglandins (PGs) such as PGE_2, which are key mediators of inflammatory hyperalgesia. As suppression of PG production by cyclooxygenase inhibitors carries the risk of GI mucosal bleeding and damage, blockade of PG receptors on sensory neurons may be a more selective strategy of preventing the proalgesic action of PGs. PGE_2 excites abdominal afferents via EP_1 receptors and sensitizes them to other algesic mediators [8]. Experiments with spinal ganglion neurons indicate that EP_1, EP_2, EP_{3C} and EP_4 receptors contribute to the PGE_2-induced sensitization [14].

Bradykinin receptors

Bradykinin is a proinflammatory and algesic mediator that can act via two types of receptor, B_1 and B_2. While the acute effects of bradykinin are mediated by B_2 receptors, B_1 receptors come into play in chronic inflammatory hyperalgesia. Bradykinin acting via B_2 receptors excites mesenteric afferent nerve fibres and contributes to acute visceral pain, this action being augmented by PGE_2. The potential of B_1 and B_2 bradykinin receptor blockade in reducing GI hyperalgesia due to infection or inflammation is borne out by a number of experimental studies [8,15].

Protease-activated receptors

Protease-activated receptors (PARs) of type PAR-2 are expressed by sensory neurons and activated by proteases such as trypsin or tryptase. PAR-2 agonists excite spinal afferents supplying the rat jejunum, evoke behavioural pain responses when administered into the pancreatic duct, sensitize abdominal afferents to capsaicin, and give rise to delayed and prolonged abdominal hyperalgesia [16]. It awaits to be proven whether PAR-2 antagonists have potential in the control of visceral hyperalgesia.

Ionotropic purinoceptors

Ionotropic P2X purinoceptors are made of several subunits ($P2X_1$ - $P2X_7$). Since $P2X_3$ receptors are upregulated in inflammatory bowel disease [17], it has been proposed that these receptors play a role in GI nociception [18].

Transient receptor potential ion channels

Transient receptor potential (TRP) ion channels represent a large family of sensory transducers with a tetrameric structure [19,20]. Among them, TRPV1, TRPV4 and TRPA1 are expressed by distinct populations of visceral sensory neurons, the “capsaicin receptor” TRPV1 being the best studied. TRPV1 behaves as a polymodal nocisensor that is excited by noxious heat, vanilloids such as capsaicin, severe acidosis and arachidonic acid-derived lipid mediators [19,20]. In addition, TRPV1 is thought to be a key molecule in afferent neuron

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hypersensitivity because its activity is enhanced by many proalgesic pathways via channel phosphorylation or rapid recruitment of a cytosolic pool of preformed channels into the cell membrane [20]. In this way TRPV1 signalling is sensitized by mild acidosis, 5-HT, PGE_2, bradykinin, PAR-2 activation and nerve growth factor. As a consequence, the temperature threshold for TRPV1 activation (43 °C) is lowered to a level permissive for channel gating at normal body temperature.

Capsaicin-induced gating of TRPV1 in the gut gives rise to pain [21], and genetic deletion of TRPV1 reduces the responsiveness of abdominal afferent neurons to acid and distension and their sensitization by 5-HT and inflammation [20]. Suppression of TRPV1 activity is hence explored as a strategy to treat visceral hyperalgesia, given that TRPV1 is upregulated in oesophagitis, painful inflammatory bowel disease and IBS [22-24]. In addition, a proportion of patients with functional dyspepsia is hypersensitive to intragastric capsaicin [25]. Taken all experimental and clinical data together, the development of TRPV1 antagonists has been pursued as a novel approach to the treatment of GI hyperalgesia [20,26]. However, two major setback have been encountered, given that TRPV1 blockers can cause hyperthermia [27] and elevate the threshold of sensing heat, exposing individuals treated with TRPV1 blockers to a “real world” burn risk [presentation by Michael Crutchlow, Merck Research Laboratories, at the 2009 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics]. The challenge, therefore, is to design therapeutic approaches that block the action of pathologically expressed or activated TRPV1 channels while sparing those TRPV1 channels that mediate physiological processes [20].

The sensory modalities of TRPV4, which is also present on visceral afferent neurons, include strong acidosis, hypo-osmolarity and mechanical stimuli. Activation of TRPV4 enhances the responses of colonic serosal and mesenteric afferent nerve fibres to mechanical stimulation, whereas deletion of TRPV4 markedly reduces their mechanosensitivity [28,29]. The sensitivity of TRPV4 to colorectal distension is enhanced by activation of PAR-2, and the mechanical hyperalgesia evoked by PAR-2 stimulation requires the presence of TRPV4 [16,29,30].

TRPA1 is a nocisensor of afferent neurons that is remarkable for its wide spectrum of chemical modalities. This property places TRPA1 in a position to survey the alimentary canal for spicy compounds present in mustard, horseradish, wasabi, garlic, onion, cinnamon, ginger, oregano, wintergreen and clove, and to detect potentially deleterious conditions arising from the presence of alkalosis, H_2S, oxidative insults (4-hydroxy-2-nonenal, H_2O_2, acetaldehyde) as well as toxic environmental stimuli such as formaldehyde, acrolein, iodoacetamide and methyl p-hydroxybenzoate. Stimulation of TRPA1 in the colon by allyl isothiocyanate or distension excites afferent neurons and elcits pain, and experimental colitis causes hypersensitivity to TRPA1 stimulation and upregulation of TRPA1 in sensory neurons [31,32]. The potential implications of TRPA1 in GI physiology and pathophysiology are extended by its presence on enterochromaffin cells and cholecystokinin-releasing cells [33,34].

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Acid-sensing ion channels

Acid-sensing ion channels (ASICs) are trimers composed of ASIC1, ASIC2 and ASIC3 subunits. These channels are gated by mild acidosis and, as gene knockout studies indicate, can function as mechanoreceptors. ASIC3 may be of particular relevance because it is selectively expressed by vagal and spinal afferent neurons [35]. This member of the ASIC family is upregulated in the colonic mucosa of patients suffering from inflammatory bowel disease [35] and, in experimental gastritis, mediates sensitization of vagal afferent pathways to gastric acid [36].

Sensory neuron-specific Na^+ channels

Voltage-gated Na^+ channels, composed of a pore-forming α-subunit and auxiliary β-subunits, are crucial for neuronal excitability and propagation of action potentials. Of the many α-subunits, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ are preferentially expressed by primary afferent neurons. Experimental gastritis, gastric ulceration and ileitis enhance the excitability of vagal and spinal afferents predominantly via an increase of $Na_v1.8$ currents. Knockout of the $Na_v1.8$ gene attenuates the behavioural reactions to colonic sensitization and prevents referred hyperalgesia which commonly accompanies visceral hyperalgesia [37,38].

Sensory neuron-specific K^+ channels

Pathological hyperexcitability of sensory neurons can result from downregulation of voltage-gated potassium (K_v) channels whose function is to repolarize the cell membrane. Some of these channels such as $K_v1.4$ seem to be selectively expressed by afferent neurons. The increase in the excitability of spinal and vagal afferents in experimental gastric ulceration and ileitis is in part attributed to a decrease in K^+ currents [39,40].

Sensory neuron-specific Ca^{2+} channels

Gabapentin and pregabalin, two anticonvulsant drugs with high affinity for the voltage-gated α2δ1 Ca^{2+} channel subunit in spinal afferents, are able to counteract the colonic hyperalgesia elicited by inflammation [41]. The contention that pregabalin-sensitive Ca^{2+} channels play a role in pathological sensitization of GI afferents is supported by clinical studies [8].

Glutamate receptors

Glutamate is the principal transmitter of primary afferent neurons, and glutamatergic transmission in the spinal cord and brainstem is mediated by ionotropic NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors as well as group I metabotropic receptors of subtype 1 and 5 [8,42]. Antagonists of NMDA and non-NMDA ionotropic glutamate receptors reduce the spinal input evoked by noxious colorectal distension, counteract the mechanical hyperalgesia induced by repeated colonic distension or colonic inflammation and inhibit the behavioural pain response to bradykinin in experimental pancreatitis [43-45]. However, the utility of NMDA receptor antagonists in pain therapy is limited because of their adverse actions on brain activity. Since the NMDA receptor antagonist memantine is able to inhibit excitation

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of pelvic afferents by colorectal distension [46] it may be that selective blockade of peripheral glutamate receptor antagonists may have some analgesic efficacy.

Calcitonin gene-related peptide receptors

Almost all spinal afferent neurons supplying the viscera of rodents express calcitonin gene-related peptide (CGRP) which appears to contribute to visceral pain transmission. Thus, mechanical hyperalgesia in the colon due to experimental inflammation or repeated distension is reversed by the CGRP receptor antagonist $CGRP_{8-37}$ [47] The analgesic potential of CGRP receptor blockade is corroborated by the discovery that nonpeptide CGRP receptor antagonists are effective in the treatment of migraine attacks.

Tachykinin receptors

Most spinal afferents supplying the viscera of rodents contain the tachykinins substance P and neurokinin A, and tachykinin NK_1, NK_2 and NK_3 receptors are expressed at many levels of the gut–brain axis. While a large number of preclinical studies attest to a role of tachykinin receptors in visceral hyperalgesia [48], clinical trials of NK_1 and NK_3 receptor antagonists failed to reveal any benefit in IBS and oesophageal hypersensitivity [49]. Results obtained with NK_2 receptor antagonists or compounds targeting more than one tachykinin receptor in visceral pain syndromes have not yet been disclosed.

α_2-Adrenoceptors

Noradrenaline inhibits the transmission of nociceptive signals in the spinal cord via activation of presynaptic α_2-adrenoceptors on sensory nerve terminals. Intrathecal administration of the α_2-adrenoceptor agonists clonidine, fadolmidine or dexmedetomidine depresses the activation of spinal neurons by distension of the normal and inflamed colon [50]. This antinociceptive activity seems to be clinically relevant, given that clonidine reduces the sensation and discomfort associated with gastric and colorectal distension [51].

Cannabinoid receptors

A possible role of endocannabinoids in pain is envisaged from the presence of CB_1 receptors on primary afferent neurons. Activation of CB_1 receptors on the central terminals of spinal afferents inhibits the release of substance P, while CB_1 receptor activation in the periphery interferes with nerve excitation by noxious stimuli [52]. Although activation of CB_1 receptors on vagal afferent pathways counteracts nausea and emesis, the usefulness of cannabinoid receptor agonists in the treatment of visceral hyperalgesia has not yet been established.

Corticotropin-releasing factor receptors

Corticotropin-releasing factor (CRF) is a mediator of stress and anxiety, traits often observed in patients with IBS. CRF_1 receptor antagonists are able to counteract colonic hypersensitivity associated with high trait anxiety and to reduce the effect of sensitization by acetic acid-evoked inflammation [53,54]. CRF_1 receptor antagonists are currently under clinical investigation for the treatment of functional GI disorders.

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Conclusions

Experimental efforts to identify molecular traits on visceral pain pathways with a potential for therapeutic exploitation have come up with many hits. However, the translation of these advances into efficacious and safe drugs has proved difficult. One challenge is to design therapeutic approaches that block the action of pathologically expressed or activated receptors and ion channels while sparing those receptors and ion channels that mediate physiological processes. This goal requires innovative approaches such as uncompetitive antagonists/blockers or compounds that interrupt the synthesis and intracellular trafficking of pathologically upregulated receptors/ion channels. In addition, given the many targets with potential relevance to hyperalgesia, the question arises as to whether modulation of a single target is therapeutically sufficient.

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Table 1
Three classes of drug targets on sensory neurons and their transmission relays

Receptors and sensors on peripheral nerve terminals
5-Hydroxytryptamine 5-HT_3 and 5-HT_4 receptors
Adenosine A_1 and A_2 receptors
Ionotropic purinoceptors of type $P2X_2$, $P2X_3$ and $P2X_{2/3}$
Transient receptor potential ion channels of type TRPV1, TRPV4, TRPM8 and TRPA1
Acid-sensing ion channels of type ASIC1, ASIC2, ASIC3 and ASIC2b/3
Bradykinin B_1 and B_2 receptors
Prostaglandin EP_1, EP_2, EP_3, EP_4 and IP receptors
Protease-activated receptors of type PAR-2
Cholecystokinin CCK_1 receptors
Corticotropin-releasing factor receptors of type CRF_1
Somatostatin SST_2 receptors
Tachykinin NK_2 and NK_3 receptors
Ionotropic (NMDA) and metabotropic (group II subtype 2 and 3) glutamate receptors μ-, κ- and δ-Opioid receptors
Cannabinoid CB_1 receptors
Orphan G protein-coupled receptors (Mrgs)
Neurotrophin receptors (TrkA)
Mechanosensitive K^+ and Ca^{2+} channels
Ion channels relevant to excitability, conduction and transmitter release
Voltage-gated Ca^{2+} channels (N-type and α2δ1)
Voltage-gated K^+ channels (K_v1.4)
Tetrodotoxin-resistant voltage-gated Na^+ channels (Na_v1.7, Na_v1.8 and Na_v1.9)
Receptors for sensory neuron transmission and for the control of transmitter release
Ionotropic (NMDA, AMPA, kainate) and metabotropic (group I subtype 1 and 5 as well as group II subtype 2 and 3) glutamate receptors
Calcitonin gene-related peptide receptors
Tachykinin NK_1, NK_2 and NK_3 receptors
$α_2$-Adrenoceptors
μ-, κ- and δ-Opioid receptors
Cannabinoid CB_1 receptors
Adenosine A_1 receptors