The role of histamine in neurogenic inflammation

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Histamine in the neurogenic inflammation

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Summary

The term "neurogenic inflammation" has been adopted to describe the local release of inflammatory mediators from neurons such as substance P and calcitonin gene related peptide. Once released, these neuropeptides cause histamine release from adjacent mast cells. In turn, histamine evokes the substance P and calcitonin gene related peptide release, thus a bidirectional link between histamine and neuropeptides in neurogenic inflammation is established. The aim of this review is to summarize the most recent findings on the role of histamine in neurogenic inflammation with particular regards to nociceptive pain as well as neurogenic inflammation in the skin, in the airways and in the bladder.

Keywords histamine, neurogenic inflammation, histamine receptors, neuropathic pain, skin, airways, bladder

Abbreviations calcitonin gene related peptide, CGRP; cell adhesion molecule, CADM; gastro-oesophageal reflux disease, GERD; histidine decarboxylase, HDC; interstitial cystitis, IC; oestrogen receptors, ERs; painful bladder syndrome, PBS; platelet-activating factor, PAF; substance P, SP; vasoactive intestinal peptide, VIP

Introduction

The term “neurogenic inflammation” describes the local release of inflammatory mediators from afferent neurons such as substance P (SP) and calcitonin gene related peptide (CGRP). Since the first evidences of a neurogenic vasodilatation in response to noxious stimuli in the skin of humans and other mammals (Schmelz M *et al*., 2001), nowadays it is recognised that neurogenic inflammation occurs also in visceral organs. The inflammatory response evoked by the activation of the sensory nerve fibres, including local vasodilatation, plasma extravasation, leukocyte and platelet adhesion, and mast cell degranulation, is brought about by neuropeptides released from peripheral endings of sensory neurons upon stimulation of the primary sensory terminals. Both SP in neurons and histamine in mast cells have a dual mediator role in neurogenic inflammation (Figure 1). In fact, as described by Foreman and Jordan (1984), injury causes activation of sensory nerve endings either directly or through the release of histamine from adjacent mast cells. The action potential generated travels orthodromically to the dorsal horn of the spinal cord, and spreads to other branches of the same neurons which will then release SP from their terminals or varicosities. The released SP, besides contributing by itself to local vasodilatation, causes histamine release from adjacent mast cells which produce flare and further activates other sensory nerve endings (Foreman JC *et al*., 1984).

Neutrophils, whose responsiveness to SP has been repeatedly demonstrated, contribute to the inflammatory soup following neurogenic inflammation. In fact, neutrophils express the SP receptors NK_1, NK_2 and NK_3, and their challenge with SP induces COX-2 expression and PGE_2 release in the nanomolar range (Gallicchio M *et al*., 2008; Gallicchio M *et al*., 2009). Furthermore, SP at micromolar concentrations primes neutrophils, thus enhancing O_2^- production evoked by platelet-activating factor (PAF) (Brunelleschi S *et al*., 1991). In the picomolar range SP still induces netrophil adhesion to human umbilical vein endothelial cells (Dianzani C *et al*., 2003).

Together with histamine, other mast cell-derived mediators (such as, serotonin, renin, adenosine, heparin, tryptase, chymase, elastase, carboxypeptidase A and B, cathepsin, b-galactosidase, b-glucoronidase, matrix metalloproteinase, chemotatactic factors for eosinophils and neutrophils, platelet derived factor, prostaglandin D_2, leukotriene B4, C4 and D4, tromboxane A2 and B2, nitric oxide, TNF-α and other cytokines, neuropeptides) contribute to the functional picture of neurogenic inflammation (Tore F *et al*., 2009). Experimental evidences support their role demonstrating their neuronal receptors.

Histamine and neurogenic inflammation: experimental evidences

The evidences for a neurogenic mechanism in the involvement of SP in the flare response stems from data showing that local anaesthetic injection into the human skin reduced the spread of the flare response although without affecting the development of the wheal response (Foreman JC *et al*., 1983). Otherwise the role of histamine has been investigated mostly by specific receptor-oriented approaches. The effects of SP on flare response in human skin are mimicked only by the neuropeptide fragments able to degranulate rat mast cells *in vitro* (Fewtrell CM *et al*., 1982). The H_1 histamine antagonist chlorpheniramine (20 mg i.v.) has been reported to prevent the spread of the flare response to SP in the human skin (Foreman JC *et al*., 1983). These first observations of the role of histamine in the neurogenic inflammation have been further elucidated thanks to immunoistochemical studies demonstrating the proximity of mast cells and nerve fibres containing neuropeptides, with first studies in dura mater and gut, while larger body of evidence is available for the skin (Nakanishi M *et al*., 2008). Moreover, Janiszewski *et al*. (1990) have demonstrated in a co-colture system that the activation of peritoneal mast cells induce depolarization and decrease membrane resistance in sympathetic neurons (Janiszewski J *et al*., 1990). A bidirectional communication between nerves and mast cells has been supported by the presence of receptors for many neuropeptides (such as vasoactive intestinal peptide, neuropeptide Y, SP, CGRP, propiomelanocortin, galanin, neuromedin U, pituary adenilate cyclise-activating polypeptide, neurotenisn and corticotrophin-releasing factor) on mast cells surface. Thus these mediators can exert both paracrine and autocrine effects on mast cells (Figure 1). Similarly, also histamine exerts autocrine effects on mast cells as they express all the histamine receptors $H_{1\text{-}4}$ (Tore F *et al*., 2009).

Notably, the interactions between mast cells and adjacent nerves is also accomplished by adhesion molecules such as N-cadherin or cell adhesion molecule (CADM)-1, a calcium-dependent adhesion protein that can be cleave by the metalloproteinase MT5-MMP of the peptidergic receptors in the dorsal root ganglion (Guillot X *et al*., 2012; Nakanishi M *et al*., 2008).

Histamine, neurogenic inflammation and nociceptive pain

While the contribution of neurogenic inflammation to nociception has been previously elucidated (Julius D *et al*., 2001), more recently detailed analysis of the role of histamine receptors has been investigated.

Mechanoinsensitive C-fibres are known to be activated by histamine and to be responsible for the neuropetide release, for example in the skin inducing the axon reflex flare (Groetzner P *et al*., 2010). Histamine-immunoreactive nerve fibres have been found in the superficial laminae of the dorsal horn, an important site for nociceptive transmission. The mRNA of histamine H_1 receptor genes has been detected in many SP and CGRP immunoreactive neurons following the peripheral nerve injuries (Kashiba H *et al*., 1999), and histamine has been reported to mediate the release of SP and glutamate in inflammatory conditions (Riedel W *et al*., 2001). Moreover, a bidirectional relationship between CGRP and histamine can be proposed according to the data showing that: CGRP induces histamine release from mast cells and potentiates histamine effects in the rat (Mobarakeh JI *et al*., 2006); intraperitoneally injection of histamine induces CGRP release into the cerebrospinal fluid (Bileviciute I *et al*., 1994); histamine administrated to the nasal mucosa causes CGRP release from peripheral terminals of trigeminal ganglion in the guinea pig (Tani E *et al*., 1990). Further support of a cooperation between histamine and CGRP is afforded by the observation of a colocalization of both the histamine H_3 receptor and CGRP on Aδ fibres; both mediators contributing to an high threshold mechanical nociceptive effect (Cannon KE *et al*., 2007).

More recently, it has been demonstrated that both the H_1 receptor antagonist pyrilamine and the H_2 receptor antagonist ranitidine produce a dose-dependent antinociceptive response in the formalin test, and that a histamine intrathecally-induced hyperalgesia has been blunted by the GCRP antagonist CGRP 8-37 (Mobarakeh JI *et al*., 2011).

Studies with histamine H_1 receptor knockout mice have demonstrated that both the receptor and its natural ligand are necessary to facilitating pain transmission at both peripheral and central levels (Mobarakeh JI *et al*., 2002; Mobarakeh JI *et al*., 2000). By using histidine decarboxylase (HDC) gene knockout mice it has been shown that the NK_1 receptors in the spinal cord mediate the histamine-induced hyperalgesic responses (Yoshida A *et al*., 2005). Several *in vivo* studies have evaluated the antinociceptive efficacy of antihistamines. The administration of H_1 and H_2 receptor antagonists, chlorpheniramine and cimetidine respectively, was found to inhibit the development of both thermal and mechanical hyperalgesia, although chlorpheniramine was more potent (Zuo Y *et al*., 2003). Even the most recently discovered histamine receptors, the H_3 and H_4 receptors, have been shown to be involved in mediating nociception. The pre-treatment with H_3/H_4 receptors dual antagonist thioperamide attenuated c48/80-induced thermal pain 30 min after challenge without causing analgesia (Chatterjea D *et al*., 2012). Moreover, it was reported that H_3 receptor antagonists, such as GSK-189254 and ABT-239, are effective in reducing allodynia and hyperalgesia in models of neuropathic, and inflammatory pain (Hsieh GC *et al*., 2010b; Medhurst AD *et al*., 2007; Medhurst SJ *et al*., 2008).

Focusing on H_4 receptors, both the experimental antagonists JNJ7777120 (10 and 30 mg kg^{-1}, s.c.) and VUF6002 (10 mg kg^{-1}, s.c.) significantly reduced the paw oedema and hyperalgesia provoked by subplantar injection of carrageenan (Coruzzi G *et al*., 2007). According to these data, JNJ7777120 reversed hyperalgesia in both acute and chronic pain models (Hsieh GC *et al*., 2010a).

Notably, the same study has reported no effect for H_1 receptor antagonist diphenhydramine, H_2 receptor antagonists ranitidine, or H_3 receptor antagonist ABT-239, thus suggesting a dominant role of the H_4 receptors in animal models of inflammatory and neuropathic pain.

All together, these data from animal models may be regarded as indicative of a potential efficacy of antihistamines in clinical setting. However, clinical evidence is still lacking and previously trials were negative (Raffa RB, 2001).

Histamine and neurogenic inflammation in the skin

The involvement of histamine in cutaneous neurogenic inflammation stems from the observation that this amine triggers the so called "triple response". Nowadays, local erythema results from the axon reflex and antidromic sensory nerve stimulation-induced release of different vasoactive mediators, not only histamine, but also SP, histamine, purines and CGRP. Itch is mediated via dedicated afferent nonmyelinated C-type nerve fibres different from the polymodal C-fibres being unresponsive to mechanical stimulation. The so called 'pruriceptors' are differentiated in histamine-sensitive and histamine-independent itch-specific C-fibres. In particular, histamine–sensitive C-fibres, about the 5% of afferent C-fibres in human cutaneous nerves, are characterized by slow conduction velocities and extensive terminal branching (Raap U *et al*., 2011; Shim WS *et al*., 2008). When activated by histamine, they transmit electrical signals to the superficial layer of the dorsal horn of the spinal cord. These signals then ascend to the thalamus through contralateral spinothalamic tracts and are eventually conducted to the somatosensory and cingulated cortex (Figure 2). All the histamine receptors are involved in mediating histamine signal on neurons, but with a different functional weight. The failure of cimetidine to suppress histamine-induced itch in BalbC mice (Bell JK *et al*., 2004) do not support an involvement of H_2 receptor in itch. The H_1 receptor is the most extensively studied. Indeed, H_1 receptor blockers have an established and valuated place in the treatment of itching of allergic and non-allergic origin (Skidgel RA *et al*., 2011).

Intriguing data on the H_3 receptor seem to contradict the aforementioned histamine-induced itch pathway (Summey BT *et al*., 2005), as antagonists such as thioperamide or AQ0145 were found to increase significantly the incidence of scratching behaviour in mice (Sugimoto Y *et al*., 2004). Histamine H_3 receptor antagonists might block the modulatory role afforded by the presinaptic H_3 receptor, thus favouring the release of neuropetides from sensory endings (Cannon KE *et al*., 2007). More recently, data obtained with clobenoprit, an H_3 receptor antagonists and H_4 receptor agonist, suggested that H_4 receptor also is involved in itch. Clobenoprit caused scratching responses in the mouse that were attenuated by pretreating animals with the H_4 receptor antagonist, JNJ7777120 (Dunford PJ *et al*., 2007). Moreover, it has been reported that H_4 receptor agonists are able to induce itch through a direct action on peripheral nerves (Bell JK *et al*., 2004), and that the H_4 antagonist inhibit SP-induced itch, which has been reported to be resistant to H_1 receptor antagonists (Yamaura K *et al*., 2009). More recently, Suwa *et al*. (2011) have demonstrated that JNJ7777120 (10 and 30 mg kg^{-1} die), and not the histamine H_1 receptor antagonist fexofenadine (30 mg kg^{-1} die), reduces the scratching behaviour and ameliorates the skin lesions induced by repeated challenge with 2,4,6-trinitrochlorobenzene in HR-1 mice, in a dose-dependent manner (Suwa E *et al*., 2011).

Interestingly, in the mice blocking both the H_1 receptors and the H_4 receptors, by a dual antagonist or a combination therapy gave the maximum response, almost completely abolish the itch response (Dunford PJ *et al*., 2007).

Besides, other published data indicate that H_1 receptors and H_4 receptors share a similar pathway in the neuron excitation by increasing intracellular Ca^{2+} levels (Shim WS *et al*., 2008). Histamine elevates calcium levels through H_1 receptor in rat cultured sensory neurons, and this effect is blocked by the PLC inhibitor U73122 (Nicolson TA *et al*., 2002).

Moreover, in mouse sensory neurons stimulated by capsaicin, histamine induces inward currents and calcium influx in a TRPV1-dependent manner, as demonstrated by the blocking effect of

TRPV1 antagonists; in keeping with these results histamine-induced scratching is significantly lower in TRPV1-deficient mice (Kajihara Y *et al*., 2010; Shim WS *et al*., 2007).

All these evidences explain at least in part the antipruritic effects of both mirtazapine and doxepin, two antidepressant that share also additional antihistaminic effects (Raap U *et al*., 2011). Moreover, the well recognised risk-benefit profile of H_1 antihistamines, especially the non-sedative second generation ones, lead the European Academy of Allergy and Clinical Immunology to recommend in its guidelines an updosing of nonsedating antihistamines up to four-fold in patients with chronic urticaria. Clinical studies on H_4 receptor antagonists are currently ongoing (Engelhardt H *et al*., 2009).

Histamine and neurogenic inflammation in the airways

Misery (2008) approached the intriguing parallelism between itch/scratching and cough starting from a common pathophysiology that involves the C fibres, the mast cells, histamine, SP and other tachykinins. Indeed, the close proximity between mast cells and the nerve endings in the lung suggests a similar neuro-immuno crosstalk (Misery L, 2008) as found in the skin. Sensory nerve endings release neuropeptides such as SP and CGRP, which induce mast cell activation and degranulation. The antidromic release of neuropeptides from nociceptors in the airways causes vasodilatation and oedema associated with nasal obstruction in the upper airways, and broncocostriction in the lower airways, as well as plasma protein exudation, mucus secretion and inflammatory cell recruitment. As a proof of neurogenic inflammation in the airways, local anaesthesia with lidocaine improved airway hyperreactivity and reduced capsaicin-induced cough (Muraki M *et al*., 2008).

A first evidence of the relationship between SP and histamine in the airways came in 1994, when Heaney *et al*. (1994) demonstrated the ability of SP to stimulate human mast cells obtained from bronchoalveolar lavage (Heaney LG *et al*., 1994). More recently, sputum SP and mast cell tryptase concentrations were remarkably increased in patients with chronic cough, and evenly increased in those with cough due to gastro-oesophageal reflux disease (GERD). These latter data suggest that GERD-induced cough may be related to a cough reflex hypersensitivity caused by neurogenic airway inflammation (Qiu Z *et al*., 2011), and are in keeping with the results obtained by Birring *et al*. (2004), who measured an increased histamine content in the sputum of patients with idiopathic chronic cough and cough variant asthma/eosinophilic bronchitis in comparison with normal subjects (Birring SS *et al*., 2004). Rat lung mast cells have been found to release histamine in response to high doses of SP *in vitro*; moreover, it has been shown that the NK_1 receptor-mediated mast cell activation partly affords for airway plasma leakagein F344-, but not in BDE-rats, exposed to SP and capsaicin. The airway responsiveness to tachykinins discriminates these two inbred strains. Actually, only the F344 presents NK_1 receptors mast cells that display a proreleasing effect (Pauwels RA *et al*., 1995). More recently, it has been reported that CP-99,994 (5 mg kg^{-1} i.v.), a NK_1 receptor antagonist, abolished the microvascular leakage elicited in the rat airways by a single inhalation of toluene-2,4-diisocyanate. On the contrary, ketotifen (1 mg kg^{-1} i.v.), provided with H_1 antagonism and mast cell-stabilizing properties, did not exert any effect in this model (Sakamoto T *et al*., 2012). In a model of microvascular leakage hypersensitivity induced in the airways of guinea-pigs aerosolised with histamine it has been demonstrated that, while NKB and the NK_3 receptor agonist senktide, enhanced airway hypersensitivity to histamine. In the same model, both the tachykinin NK_3 receptor antagonists osanetant and the NK_1 receptor antagonist nolpitantium were able to abolish the histamine-induced microvascular leakage. NK2 ligands were uneffective (Daoui S *et al*., 2001). Moreover, it has been reported that toluene-2,4-diisocyanate exposure causes an increase in histamine content, HDC activity and gene expression in the nasal mucosa of sensitized rats (Kitamura Y *et al*., 2004). Olopatadine hydrochloride, an H_1 receptor antagonist, besides inhibiting the capsaicin-induced sneezing response, has been found to inhibit antigen-induced sneeze and nasal rubbing responses in both wild-type and H_1 receptor-deficient mice, although at very high doses (Tamura T *et al*., 2008), thus suggesting a H_1 receptor independent effect. Indeed, these data, together with the failure of cetirizine to inhibit completely these responses in H_1

receptor-deficient mice (Kayasuga R *et al*., 2002; Sugimoto Y *et al*., 2004), could lead to hypothesise the involvement of other receptors in these responses.

Histamine and neurogenic inflammation in the bladder

Interstitial cystitis (IC), or painful bladder syndrome (PBS), numbers among its causes neurogenic inflammation; in fact, an increased density of nerve fibres has been reported (Peeker R *et al*., 2000). Evidences from both rodent and humans highlight an important role for mast cells. Activated mast cells have been associated to the rodent neurogenic cystitis induced by the Bartha strain of pseudorabies virus (PRV) (Chen MC *et al*., 2006; Jasmin L *et al*., 2000). Moreover, clinical studies have demonstrated elevated mast cell number in the lamina propria of IC bladder biopsies (Leiby BE *et al*., 2007) and an increased urinary histamine metabolites (el-Mansoury M *et al*., 1994). Although the central role of mast cells in PBS/IC is still unclear, *in vivo* model of IC pathogenesis suggested a positive feedback loop with SP containing peripheral nerves and mast cells: the activation of the bladder-associated circuits in the CNS initiates SP release by peripheral nerves in the bladder leading SP-mediated mast cell activation. Consequently, mast cell degranulation induces bladder inflammation by acting on urothelium. Histamine contribute to IC/PBS, is not only in evoking an inflammatory response, but seems also to be related to pelvic pain. In fact, histamine and histamine receptors as mediators in pain responses have been described in both animal models and humans (Mobarakeh JI *et al*., 2006; Thilagarajah R *et al*., 2001). Although the specific cell type among mast cells, basophils, neutrophils, dendritic cells and histaminergic neurons regulating histamine-mediated pain is unknown, it has been demonstrated, by using a model of PRV-induced pelvic pain in mast cell deficient $Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ mice, that mast cells are required for histamine-mediated pelvic pain (Rudick 2008). However, the same authors demonstrated that $Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ mice reconstituted with $HDC^{-/-}$bone marrow exhibited diminished pain, thus suggesting that non-mast cell sources of histamine may also contribute to pain. Moreover, Rudick CN *et al.* (2008) demonstrated that PRV induced pelvic pain is independent from TNF-dependent pathology and instead is mediated by mast cell histamine, which then induces pain via histamine receptors H_1 and H_2 (Rudick CN *et al*., 2008). Thus, it has been suggested that antagonists of histamine H_1 and H_2 receptors are candidates for clinical trials in the treatment of chronic pain conditions, such as IC-related pelvic pain. Indeed, pilot clinical studies suggest that antihistamine therapy could be effective on IC-related pelvic pain. In particular, a symptomatic improvement has been reported in 30% of patients treated with the H_1 receptor antagonist hydroxyzine hydrochloride from 25 mg/die at night to 50 mg at night + 25 mg in the morning over a 2-week period (Theoharides TC *et al*., 1997). Although these positive results suggest a therapeutic role of histamine H_1 receptor antagonist in the treatment of IC/PBS, further studies with newer generation histamine H_1 receptor antagonists, with a lesser sedation component, have to be conducted. Moreover, the histamine H_2 receptor antagonist cimetidine produced significant improvement in pain and nocturia in a limited trial of PBS patients (Thilagarajah R *et al*., 2001). It has to be stressed that approximately 90% of patients with PBS/IC are women, thus suggesting that the process involving mast cells may be hormonally influenced. In fact, oestrogen receptors (ERs) are expressed on human mast cells and can mediate their degranulation, while the ER antagonist tamoxifen inhibits this fenomenon (Rudick CN *et al*., 2012).

All together these findings suggest that reproductive hormones may modulate IC symptoms at the mast cell levels. This hypothesis has been recently tested by Rudick CN *et al*. (2012) who assessed the basis of gender specific pelvic pain in the murine model of neurogenic cystitis PRV-induced. The data obtained suggest that pelvic pain in mice with murine neurogenic cystitis is mediated by gender specific responsiveness to mast cells, in contrast pelvic pain severity resulted to be modulated by genetic factors (Rudick CN *et al*., 2012).

Conclusion

In conclusion, experimental data here included widely show the complex physiopatological mechanism(s) known as neurogenic inflammation and the key role played by histamine (Table 1).

Neurogenic inflammation is involved in several processes of animal and human physiopathology: this review, with no ambition to be completely exhaustive, has anyway outlined the most up-to-date and widest fields of investigation. A comprehensive evaluation of the histamine role in neurogenic inflammation, as discussed here, highlights how the many experimental evidences have not yet reached a full clinical transferability and not yet support new pharmacotherapeutic approaches.

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Conflict of interest

None.

References

Bell JK, McQueen DS, Rees JL (2004) Involvement of histamine H4 and H1 receptors in scratching induced by histamine receptor agonists in Balb C mice. Br J Pharmacol 142: 374-380.

Bileviciute I, Lundeberg T, Ekblom A, Theodorsson E (1994) Substance P-, neurokinin A-, calcitonin gene-related peptide- and neuropeptide Y-like immunoreactivity (-LI) in rat knee joint synovial fluid during acute monoarthritis is not correlated with concentrations of neuropeptide-LI in cerebrospinal fluid and plasma. Neurosci Lett 167: 145-148.

Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID (2004) Induced sputum inflammatory mediator concentrations in chronic cough. Am J Respir Crit Care Med 169: 15-19.

Brunelleschi S, Tarli S, Giotti A, Fantozzi R (1991) Priming effects of mammalian tachykinins on human neutrophils. Life Sci 48: PL1-5.

Cannon KE, Chazot PL, Hann V, Shenton F, Hough LB, Rice FL (2007) Immunohistochemical localization of histamine H3 receptors in rodent skin, dorsal root ganglia, superior cervical ganglia, and spinal cord: potential antinociceptive targets. Pain 129: 76-92.

Chatterjea D, Wetzel A, Mack M, Engblom C, Allen J, Mora-Solano C, et al. (2012) Mast cell degranulation mediates compound 48/80-induced hyperalgesia in mice. Biochem Biophys Res Commun 425: 237-243.

Chen MC, Blunt LW, Pins MR, Klumpp DJ (2006) Tumor necrosis factor promotes differential trafficking of bladder mast cells in neurogenic cystitis. J Urol 175: 754-759.

Coruzzi G, Adami M, Guaita E, de Esch IJ, Leurs R (2007) Antiinflammatory and antinociceptive effects of the selective histamine H4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. Eur J Pharmacol 563: 240-244.

Daoui S, Ahnaou A, Naline E, Emonds-Alt X, Lagente V, Advenier C (2001) Tachykinin NK(3) receptor agonists induced microvascular leakage hypersensitivity in the guinea-pig airways. Eur J Pharmacol 433: 199-207.

Dianzani C, Collino M, Lombardi G, Garbarino G, Fantozzi R (2003) Substance P increases neutrophil adhesion to human umbilical vein endothelial cells. Br J Pharmacol 139: 1103-1110.

Dunford PJ, Williams KN, Desai PJ, Karlsson L, McQueen D, Thurmond RL (2007) Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. J Allergy Clin Immunol 119: 176-183.

el-Mansoury M, Boucher W, Sant GR, Theoharides TC (1994) Increased urine histamine and methylhistamine in interstitial cystitis. J Urol 152: 350-353.

Engelhardt H, Smits RA, Leurs R, Haaksma E, de Esch IJ (2009) A new generation of anti-histamines: Histamine H4 receptor antagonists on their way to the clinic. Curr Opin Drug Discov Devel 12: 628-643.

Fewtrell CM, Foreman JC, Jordan CC, Oehme P, Renner H, Stewart JM (1982) The effects of substance P on histamine and 5-hydroxytryptamine release in the rat. J Physiol 330: 393-411.

Foreman JC, Jordan CC (1984) Neurogenic inflammation. Trends in Pharmacological Sciences 5: 116-119.

Foreman JC, Jordan CC, Oehme P, Renner H (1983) Structure-activity relationships for some substance P-related peptides that cause wheal and flare reactions in human skin. J Physiol 335: 449-465.

Gallicchio M, Benetti E, Rosa AC, Fantozzi R (2008) Substance P-induced cycloxygenase-2 expression in polymorphonuclear cells. Inflamm Res 57 Suppl 1: S17-18.

Gallicchio M, Benetti E, Rosa AC, Fantozzi R (2009) Tachykinin receptor modulation of cyclooxygenase-2 expression in human polymorphonuclear leucocytes. Br J Pharmacol 156: 486-496.

Groetzner P, Weidner C (2010) The human vasodilator axon reflex - an exclusively peripheral phenomenon? Pain 149: 71-75.

Guillot X, Semerano L, Decker P, Falgarone G, Boissier MC (2012) Pain and immunity. Joint Bone Spine 79: 228-236.

Heaney LG, Cross LJ, Stanford CF, Ennis M (1994) Differential reactivity of human bronchoalveolar lavage mast cells to substance P. Agents Actions 41 Spec No: C19-21.

Hsieh GC, Chandran P, Salyers AK, Pai M, Zhu CZ, Wensink EJ, et al. (2010a) H4 receptor antagonism exhibits anti-nociceptive effects in inflammatory and neuropathic pain models in rats. Pharmacol Biochem Behav 95: 41-50.

Hsieh GC, Honore P, Pai M, Wensink EJ, Chandran P, Salyers AK, et al. (2010b) Antinociceptive effects of histamine H3 receptor antagonist in the preclinical models of pain in rats and the involvement of central noradrenergic systems. Brain Res 1354: 74-84.

Janiszewski J, Bienenstock J, Blennerhassett MG (1990) Activation of rat peritoneal mast cells in coculture with sympathetic neurons alters neuronal physiology. Brain Behav Immun 4: 139-150.

Jasmin L, Janni G, Ohara PT, Rabkin SD (2000) CNS induced neurogenic cystitis is associated with bladder mast cell degranulation in the rat. J Urol 164: 852-855.

Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413: 203-210.

Kajihara Y, Murakami M, Imagawa T, Otsuguro K, Ito S, Ohta T (2010) Histamine potentiates acid-induced responses mediating transient receptor potential V1 in mouse primary sensory neurons. Neuroscience 166: 292-304.

Kashiba H, Fukui H, Morikawa Y, Senba E (1999) Gene expression of histamine H1 receptor in guinea pig primary sensory neurons: a relationship between H1 receptor mRNA-expressing neurons and peptidergic neurons. Brain Res Mol Brain Res 66: 24-34.

Kayasuga R, Sugimoto Y, Watanabe T, Kamei C (2002) Participation of chemical mediators other than histamine in nasal allergy signs: a study using mice lacking histamine H(1) receptors. Eur J Pharmacol 449: 287-291.

Kitamura Y, Miyoshi A, Murata Y, Kalubi B, Fukui H, Takeda N (2004) Effect of glucocorticoid on upregulation of histamine H1 receptor mRNA in nasal mucosa of rats sensitized by exposure to toluene diisocyanate. Acta Otolaryngol 124: 1053-1058.

Leiby BE, Landis JR, Propert KJ, Tomaszewski JE (2007) Discovery of morphological subgroups that correlate with severity of symptoms in interstitial cystitis: a proposed biopsy classification system. J Urol 177: 142-148.

Medhurst AD, Atkins AR, Beresford IJ, Brackenborough K, Briggs MA, Calver AR, et al. (2007) GSK189254, a novel H3 receptor antagonist that binds to histamine H3 receptors in Alzheimer's disease brain and improves cognitive performance in preclinical models. J Pharmacol Exp Ther 321: 1032-1045.

Medhurst SJ, Collins SD, Billinton A, Bingham S, Dalziel RG, Brass A, et al. (2008) Novel histamine H3 receptor antagonists GSK189254 and GSK334429 are efficacious in surgically-induced and virally-induced rat models of neuropathic pain. Pain 138: 61-69.

Misery L (2008) Are pruritus and scratching the cough of the skin? Dermatology 216: 3-5.

Mobarakeh JI, Sakurada S, Hayashi T, Orito T, Okuyama K, Sakurada T, et al. (2002) Enhanced antinociception by intrathecally-administered morphine in histamine H1 receptor gene knockout mice. Neuropharmacology 42: 1079-1088.

Mobarakeh JI, Sakurada S, Katsuyama S, Kutsuwa M, Kuramasu A, Lin ZY, et al. (2000) Role of histamine H(1) receptor in pain perception: a study of the receptor gene knockout mice. Eur J Pharmacol 391: 81-89.

Mobarakeh JI, Takahashi K, Sakurada S, Kuramasu A, Yanai K (2006) Enhanced antinociceptive effects of morphine in histamine H2 receptor gene knockout mice. Neuropharmacology 51: 612-622.

Mobarakeh JI, Torkaman-Boutorabi A, Rahimi AA, Ghasri S, Nezhad RM, Hamzely A, et al. (2011) Interaction of histamine and calcitonin gene-related peptide in the formalin induced pain perception in rats. Biomed Res 32: 195-201.

Muraki M, Iwanaga T, Haraguchi R, Kubo H, Tohda Y (2008) Continued inhalation of lidocaine suppresses antigen-induced airway hyperreactivity and airway inflammation in ovalbumin-sensitized guinea pigs. Int Immunopharmacol 8: 725-731.

Nakanishi M, Furuno T (2008) Molecular basis of neuroimmune interaction in an in vitro coculture approach. Cell Mol Immunol 5: 249-259.

Nicolson TA, Bevan S, Richards CD (2002) Characterisation of the calcium responses to histamine in capsaicin-sensitive and capsaicin-insensitive sensory neurones. Neuroscience 110: 329-338.

Pauwels RA, Germonpre PR, Kips JC, Joos GF (1995) Genetic control of indirect airway responsiveness in the rat. Clin Exp Allergy 25 Suppl 2: 55-60.

Peeker R, Aldenborg F, Dahlstrom A, Johansson SL, Li JY, Fall M (2000) Increased tyrosine hydroxylase immunoreactivity in bladder tissue from patients with classic and nonulcer interstitial cystitis. J Urol 163: 1112-1115.

Qiu Z, Yu L, Xu S, Liu B, Zhao T, Lu H (2011) Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. Respirology 16: 645-652.

Raap U, Stander S, Metz M (2011) Pathophysiology of itch and new treatments. Curr Opin Allergy Clin Immunol 11: 420-427.

Raffa RB (2001) Antihistamines as analgesics. J Clin Pharm Ther 26: 81-85.

Riedel W, Neeck G (2001) Nociception, pain, and antinociception: current concepts. Z Rheumatol 60: 404-415.

Rudick CN, Bryce PJ, Guichelaar LA, Berry RE, Klumpp DJ (2008) Mast cell-derived histamine mediates cystitis pain. PLoS One 3: e2096.

Rudick CN, Pavlov VI, Chen MC, Klumpp DJ (2012) Gender specific pelvic pain severity in neurogenic cystitis. J Urol 187: 715-724.

Sakamoto T, Kamijima M, Miyake M (2012) Neurogenic airway microvascular leakage induced by toluene inhalation in rats. Eur J Pharmacol 685: 180-185.

Schmelz M, Petersen LJ (2001) Neurogenic inflammation in human and rodent skin. News Physiol Sci 16: 33-37.

Shim WS, Oh U (2008) Histamine-induced itch and its relationship with pain. Mol Pain 4: 29.

Shim WS, Tak MH, Lee MH, Kim M, Koo JY, Lee CH, et al. (2007) TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. J Neurosci 27: 2331-2337.

Skidgel RA, Kaplan AP, Erdös EG (2011) Histamine, Bradykinin, and Their Antagonists. In: Brunton LL (ed). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th edn. The McGraw-Hill Companies, Inc. pp 911-935.

Sugimoto Y, Iba Y, Nakamura Y, Kayasuga R, Kamei C (2004) Pruritus-associated response mediated by cutaneous histamine H3 receptors. Clin Exp Allergy 34: 456-459.

Summey BT, Yosipovitch G (2005) Pharmacologic advances in the systemic treatment of itch. Dermatol Ther 18: 328-332.

Suwa E, Yamaura K, Oda M, Namiki T, Ueno K (2011) Histamine H(4) receptor antagonist reduces dermal inflammation and pruritus in a hapten-induced experimental model. Eur J Pharmacol 667: 383-388.

Tamura T, Komai M (2008) Effect of olopatadine hydrochloride, an anti-histamine drug, on rhinitis induced by intranasal instillation of toluene-2,4-diisocyanate in rats. Int Immunopharmacol 8: 916-921.

Tani E, Senba E, Kokumai S, Masuyama K, Ishikawa T, Tohyama M (1990) Histamine application to the nasal mucosa induces release of calcitonin gene-related peptide and substance P from peripheral terminals of trigeminal ganglion: a morphological study in the guinea pig. Neurosci Lett 112: 1-6.

Theoharides TC, Sant GR (1997) Hydroxyzine therapy for interstitial cystitis. Urology 49: 108-110.

Thilagarajah R, Witherow RO, Walker MM (2001) Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. BJU Int 87: 207-212.

Tore F, Tuncel N (2009) Mast cells: target and source of neuropeptides. Curr Pharm Des 15: 3433-3445.

Yamaura K, Oda M, Suwa E, Suzuki M, Sato H, Ueno K (2009) Expression of histamine H4 receptor in human epidermal tissues and attenuation of experimental pruritus using H4 receptor antagonist. J Toxicol Sci 34: 427-431.

Yoshida A, Mobarakeh JI, Sakurai E, Sakurada S, Orito T, Kuramasu A, et al. (2005) Intrathecally-administered histamine facilitates nociception through tachykinin NK1 and histamine H1 receptors: a study in histidine decarboxylase gene knockout mice. Eur J Pharmacol 522: 55-62.

Zuo Y, Perkins NM, Tracey DJ, Geczy CL (2003) Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. Pain 105: 467-479.

Table 1. Effect of selective histamine receptor antagonism in neurogenic inflammation

Effect	**Histamine receptor subtype**			
	H_1R	**H_2R**	**H_3R**	**H_4R**
Pain	↓	↓	↓	↓
Hyperalgesia*	↓	↓	↓	↓
Allodynia	?	?	↓	?
Itch	↓	↔	↑	↓
Sneezing response	↓**	?	?	?

*The differential involvement of histamine receptor subtypes has been demonstrated by different experimental models

**only at high doses

Legends

Figure 1. The dual mediator role of mast cells: bidirectional interaction nerves-mast cells. Neuropeptide released from sensory nerve endings stimulate adjacent mast cells in a receptor dependent manner. Mediators released from mast cells act in both a paracrine and autocrine fashion. CGRP= calcitonin gene related peptide; SP= substance P; VIP= vasoactive intestinal peptide

Figure 2. The itch system. Histamine released from mast cells after a local stimulus activates histamine-sensitive pruriceptors, thus generating an actions potential which orthodromically travels, through to the dorsal horn of the spinal cord and the thalamus, to the cortex (blue line). The following antidromic stimulation induces the release of different mediators from sensory endings, substance P (SP) and calcitonin gene related peptide (CGRP). SP and CGRP released causes further mast cells degranulation resulting in vasodilatation (flare) and the recruitment of other pruriceptors.