

**REVIEW****The role of histamine in neurogenic inflammation**

A C Rosa and R Fantozzi

*Dipartimento di Scienza e Tecnologia del Farmaco, University of Turin, Turin, Italy***Correspondence**Arianna Carolina Rosa,  
Dipartimento di Scienza e  
Tecnologia del Farmaco,  
University of Turin, Via P. Giuria  
9, Turin 10125, Italy. E-mail:  
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The term 'neurogenic inflammation' has been adopted to describe the local release of inflammatory mediators, such as substance P and calcitonin gene-related peptide, from neurons. Once released, these neuropeptides induce the release of histamine from adjacent mast cells. In turn, histamine evokes the release of substance P and calcitonin gene-related peptide; 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 regard to nociceptive pain, as well as neurogenic inflammation in the skin, airways and bladder.

**LINKED ARTICLES**

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**Abbreviations**

CGRP, calcitonin gene-related peptide; ERs, oestrogen receptors; GERD, gastro-oesophageal reflux disease; HDC, histidine decarboxylase; IC, interstitial cystitis; PBS, painful bladder syndrome; SP, substance P; VIP, vasoactive intestinal peptide

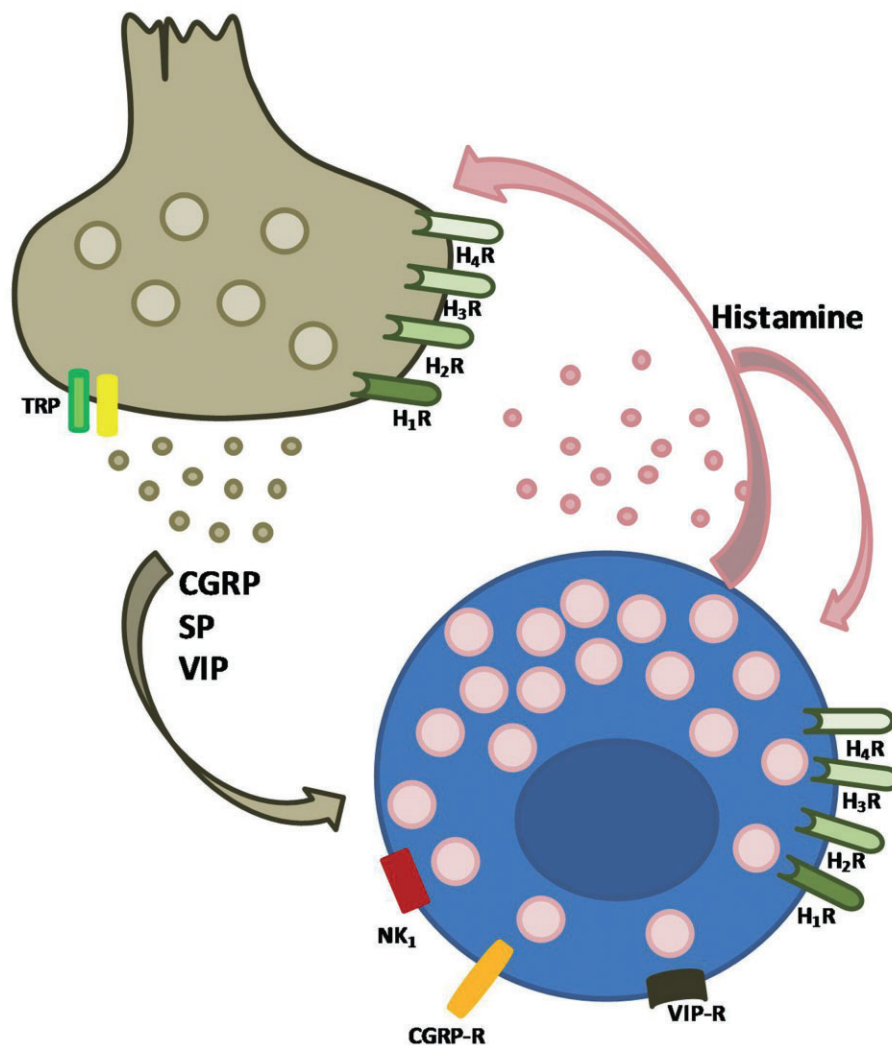
**Introduction**

The term 'neurogenic inflammation' describes the local release of inflammatory mediators, such as substance P (SP) and calcitonin gene-related peptide (CGRP), from afferent neurons. The initial evidence for neurogenic vasodilatation in response to noxious stimuli was obtained in the skin of humans and other mammals (Schmelz and Petersen, 2001), but now it is recognized that neurogenic inflammation also occurs in visceral organs. The inflammatory response evoked by the activation of the sensory nerve fibres, which includes local vasodilatation, plasma extravasation, leukocyte and platelet adhesion, and mast cell degranulation, is brought about by neuropeptides released from the 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 demonstrated by Foreman and Jordan (1984), injury causes activation of sensory nerve endings either directly or through the release of histamine from the 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, as well as contributing itself to local vasodilatation, induces histamine release from the adjacent mast cells, which produces flare and further activates other sensory nerve endings (Foreman *et al.*, 1983).

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<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>, and when stimulated with SP induce the expression of COX-2 and PGE<sub>2</sub> release in the nanomolar range (Gallicchio *et al.*, 2008; 2009). Furthermore, SP at micromolar concentrations primes neutrophils, thus enhancing O<sub>2</sub><sup>-</sup> production evoked by platelet-activating factor (Brunelleschi *et al.*, 1991). In the picomolar range, SP is still able to induce neutrophil adhesion to HUVEC (Dianzani *et al.*, 2003).

Together with histamine, other mast cell-derived mediators (such as 5-HT, renin, adenosine, heparin, tryptase, chymase, elastase, carboxypeptidase A and B, cathepsin, β-galactosidase, β-glucuronidase, MMP, chemotactic factors for eosinophils and neutrophils, platelet-derived factor,



**Figure 1**

The dual mediator role of mast cells: bidirectional interaction of nerves with mast cells. Neuropeptides released from sensory nerve endings stimulate the adjacent mast cells in a receptor-dependent manner. Mediators released from mast cells act in both a paracrine and an autocrine fashion.

PGD<sub>2</sub>, LT B<sub>4</sub>, C<sub>4</sub> and D<sub>4</sub>, TXA<sub>2</sub> and B<sub>2</sub>, NO, TNF- $\alpha$  and other cytokines and neuropeptides) contribute to the functional picture of neurogenic inflammation (Tore and Tuncel, 2009). Experimental evidence supports the role of these mediators in inflammation, demonstrating the presence of their neuronal receptors.

### Histamine and neurogenic inflammation: experimental evidence

The evidence for the involvement of a neurogenic mechanism in the SP-induced flare response stems from data showing that a local anaesthetic injection into human skin reduced the spread of the flare response, but without affecting the development of the wheal response (Foreman *et al.*, 1983). Likewise, the role of histamine has been investigated mostly using specific receptor-orientated approaches. The

effects of SP on the flare response in human skin can only be mimicked by its neuropeptide fragments that are able to degranulate rat mast cells *in vitro* (Fewtrell *et al.*, 1982). Also, the H<sub>1</sub> histamine antagonist chlorpheniramine (20 mg, i.v.) has been shown to prevent the spread of the flare response to SP in the human skin (Foreman *et al.*, 1983). Thanks to immunohistochemical studies demonstrating the proximity of mast cells and nerve fibres containing neuropeptides, these initial observations on the role of histamine in the neurogenic inflammation have been further elucidated. Preliminary studies were performed in the dura mater and gut, whereas now most of the evidence comes from experiments using skin (Nakanishi and Furuno, 2008). Moreover, Janiszewski *et al.* (1990) demonstrated, using a co-culture system, that the activation of peritoneal mast cells induces depolarization and decreases membrane resistance in sympathetic neurons (Janiszewski *et al.*, 1990). Furthermore, the notion of a bidirectional communication between nerves and

mast cells is supported by the presence of receptors for numerous neuropeptides on the surface of mast cells; these include vasoactive intestinal peptide (VIP), neuropeptide Y, SP, CGRP, pro-opiomelanocortin, galanin, neuromedin U, pituitary adenylate cyclase-activating polypeptide, neurotensin and corticotropin-releasing factor. Thus, these mediators can exert both paracrine and autocrine effects on mast cells (Figure 1). Similarly, histamine also exerts autocrine effects on mast cells as mast cells have been shown to express histamine receptors  $H_{1-4}$  (Tore and Tuncel, 2009).

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

## Histamine, neurogenic inflammation and nociceptive pain

While the contribution of neurogenic inflammation to nociception was elucidated some time ago (Julius and Basbaum, 2001), more recently, detailed analysis of the role of histamine receptors has been investigated.

Mechano-insensitive C-fibres are known to be activated by histamine and are responsible for the neuropeptide release, for example, in the skin they have been shown to induce the axon reflex flare response (Groetzner and Weidner, 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 peripheral nerve injuries (Kashiba *et al.*, 1999), and histamine has been shown to mediate the release of SP and glutamate in inflammatory conditions (Riedel and Neeck, 2001). Moreover, a bidirectional relationship between CGRP and histamine has been proposed. This is based on data showing that (i) CGRP induces histamine release from mast cells and potentiates histamine effects in the rat (Mobarakeh *et al.*, 2006); (ii) an i.p. injection of histamine induces CGRP release into the CSF (Bileviciute *et al.*, 1994) and (iii) histamine administered to the nasal mucosa causes CGRP release from the peripheral terminals of trigeminal ganglion in the guinea pig (Tani *et al.*, 1990). Further support for this link between histamine and CGRP is attained from the observed co-localization of the histamine  $H_3$  receptor with CGRP on A $\delta$  fibres, with both mediators contributing to a high-threshold mechanical nociceptive effect (Cannon *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 dose-dependent antinociceptive responses in the formalin test, and that hyperalgesia induced by intrathecal administration of histamine is attenuated by the CGRP antagonist CGRP 8-37 (Mobarakeh *et al.*, 2011).

Studies with histamine  $H_1$  receptor knockout mice have demonstrated that both the receptor and its natural ligand are needed to facilitate pain transmission at both the peripheral and central levels (Mobarakeh *et al.*, 2000; 2002). In

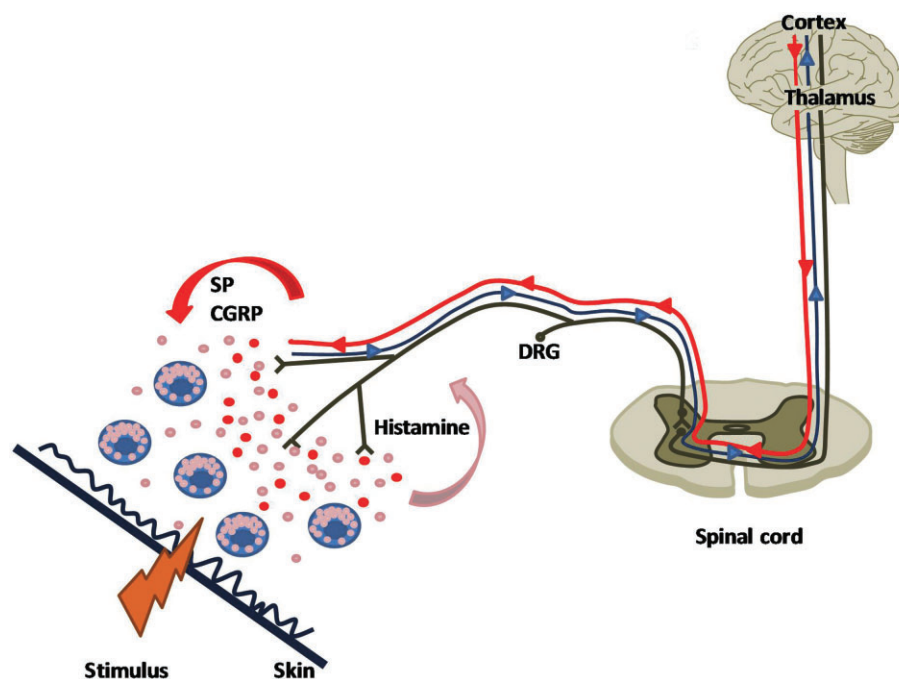
addition, using histidine decarboxylase (HDC) gene knockout mice, it was shown that  $NK_1$  receptors in the spinal cord mediate the histamine-induced hyperalgesic responses (Yoshida *et al.*, 2005). The antinociceptive efficacy of antihistamines have been evaluated in several *in vivo* studies. The 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 *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. Pretreatment with the dual  $H_3/H_4$  receptor antagonist thioperamide attenuated c48/80-induced thermal pain 30 min after the challenge without causing analgesia (Chatterjea *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 (Medhurst *et al.*, 2007; 2008; Hsieh *et al.*, 2010b).

Focusing on  $H_4$  receptors, both the experimental antagonists JNJ7777120 (10 and 30 mg·kg<sup>-1</sup>, s.c.) and VUF6002 (10 mg·kg<sup>-1</sup>, s.c.) significantly reduced the paw oedema and hyperalgesia induced by a subplantar injection of carrageenan (Coruzzi *et al.*, 2007). According to these data, JNJ7777120 reversed hyperalgesia in both acute and chronic pain models (Hsieh *et al.*, 2010a). Notably, in the same study it was found that the  $H_1$  receptor antagonist diphenhydramine,  $H_2$  receptor antagonist ranitidine or  $H_3$  receptor antagonist ABT-239 had no effect on this hyperalgesia, suggesting a dominant role for the  $H_4$  receptor in animal models of inflammatory and neuropathic pain.

Taken together, these data from animal models may be regarded as indicative of a potential efficacy of antihistamines in the clinical setting. However, clinical evidence is still lacking and previous trials obtained negative results (Raffa, 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 is known to result 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. The itching sensation is mediated by dedicated afferent non-myelinated C-type nerve fibres, which are different from the polymodal C-fibres as they are 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, which constitute about 5% of the afferent C-fibres in human cutaneous nerves, are characterized by slow conduction velocities and extensive terminal branching (Shim and Oh, 2008; Raap *et al.*, 2011). 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



**Figure 2**

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

spinothalamic tracts and are eventually conducted to the somatosensory and cingulate cortex (Figure 2). All of the histamine receptors are involved in mediating the histamine signal in neurons, but to different extents. The failure of cimetidine to suppress histamine-induced itch in Balb/C mice (Bell *et al.*, 2004) indicates that  $H_2$  receptors are not involved in itch. The  $H_1$  receptor is the most extensively histamine receptor studied. Indeed,  $H_1$  receptor blockers have an established and valued place in the treatment of itching of allergic and non-allergic origin (Skidgel *et al.*, 2011).

However, intriguing data on the  $H_3$  receptor seem to contradict the aforementioned histamine-induced itch pathway (Summey and Yosipovitch, 2005); antagonists such as thioperamide and AQ0145 were found to increase significantly the incidence of scratching behaviour in mice (Sugimoto *et al.*, 2004). It is possible that these histamine  $H_3$  receptor antagonists block the modulatory role of the presynaptic  $H_3$  receptor, thus favouring the release of neuropeptides from sensory endings (Cannon *et al.*, 2007). More recently, data obtained with clobenpropit, an  $H_3$  receptor antagonist and  $H_4$  receptor agonist, suggest that the  $H_4$  receptor is also involved in itch. Clobenpropit induced scratching responses in the mouse that were attenuated by pretreating the animals with the  $H_4$  receptor antagonist, JNJ777120 (Dunford *et al.*, 2007). Moreover, it has been reported that  $H_4$  receptor agonists are able to induce itch through a direct action on the peripheral nerves (Bell *et al.*, 2004), and that  $H_4$  antagonists inhibit SP-induced itch, which has been found to be resistant to  $H_1$  receptor antagonists (Yamaura *et al.*, 2009). More recently, Suwa *et al.* (2011) demonstrated that JNJ777120 (10 and

30 mg·kg<sup>-1</sup> day), but not the histamine  $H_1$  receptor antagonist fexofenadine (30 mg·kg<sup>-1</sup> day), reduces the scratching behaviour and ameliorates the skin lesions induced by repeated challenge with 2,4,6-trinitrochlorobenzene in hairless mice, in a dose-dependent manner (Suwa *et al.*, 2011).

Interestingly, in mice, blocking both the  $H_1$  receptors and the  $H_4$  receptors with a dual antagonist or a combination of drugs gave the maximum response; it almost completely abolished the itch response (Dunford *et al.*, 2007).

In addition, other published data indicate that  $H_1$  and  $H_4$  receptors share a similar pathway, in that they stimulate neurons by increasing intracellular  $Ca^{2+}$  levels (Shim and Oh, 2008). The histamine-induced increase in calcium levels is mediated through  $H_1$  receptors in rat cultured sensory neurons, and this effect is blocked by the PLC inhibitor U73122 (Nicolson *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 inhibitory effects of TRPV1 antagonists. In keeping with these results, histamine-induced scratching is significantly lower in TRPV1-deficient mice (Shim *et al.*, 2007; Kajihara *et al.*, 2010).

All these data explain, at least in part, the antipruritic effects of mirtazapine and doxepin, two antidepressants that also have additional antihistamine effects (Raap *et al.*, 2011). Moreover, the well-recognized risk-benefit profile of  $H_1$  antihistamines, especially the non-sedative second generation ones, has led the European Academy of Allergy and Clinical Immunology to recommend, in its guidelines, the use of a maximum dose of non-sedating antihistamines up to four-

fold higher in patients with chronic urticaria. Clinical studies on H<sub>4</sub> receptor antagonists are currently ongoing (Engelhardt *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 neuroimmuno crosstalk (Misery, 2008), as that 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, which are associated with nasal obstruction in the upper airways and bronchoconstriction 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, it was shown that local anaesthesia with lidocaine improved airway hyperreactivity and reduced capsaicin-induced cough (Muraki *et al.*, 2008).

The first evidence of a relationship between SP and histamine in the airways came in 1994, when Heaney *et al.* demonstrated that SP is able to stimulate human mast cells obtained from bronchoalveolar lavage (Heaney *et al.*, 1994). More recently, sputum SP and mast cell tryptase concentrations were found to be markedly increased in patients with chronic cough, and were even elevated in those patients 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 *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. 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<sub>1</sub> receptor-mediated mast cell activation partly accounts for the airway plasma leakage in F344-, but not in BDE-rats, exposed to SP and capsaicin. The airway responsiveness to tachykinins differentiates these two inbred strains, and, in fact only the F344 strain presents NK<sub>1</sub> receptor mast cells that display a pro-releasing effect (Pauwels *et al.*, 1995). More recently, it has been reported that CP-99 994 (5 mg·kg<sup>-1</sup>, i.v.), an NK<sub>1</sub> receptor antagonist, abolishes the microvascular leakage elicited in rat airways by a single inhalation of toluene-2,4-diisocyanate. In contrast, ketotifen (1 mg·kg<sup>-1</sup>, i.v.), an H<sub>1</sub> antagonist with mast cell-stabilizing properties, did not have any effect in this model (Sakamoto *et al.*, 2012). In a guinea pig model of microvascular leakage where hypersensitivity was induced in the airways of guinea-pigs treated with aerosolized histamine, it was demonstrated that, while NKB and the NK<sub>3</sub> receptor agonist senktide, enhanced airway hypersensitivity to histamine, both the tachykinin NK<sub>3</sub> receptor antagonist osanentan

and the NK<sub>1</sub> receptor antagonist nolpitantium were able to abolish the histamine-induced microvascular leakage. In the same model, NK<sub>2</sub> ligands were found to be ineffective (Daoui *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 *et al.*, 2004). Olopatadine hydrochloride, an H<sub>1</sub> 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<sub>1</sub> receptor-deficient mice, although at very high doses (Tamura and Komai, 2008), thus suggesting it has an effect that is not dependent on H<sub>1</sub> receptors. Indeed, these data, together with the failure of cetirizine to inhibit completely these responses in H<sub>1</sub> receptor-deficient mice (Kayasuga *et al.*, 2002; Sugimoto *et al.*, 2004), indicate that other receptors may be involved in these responses.

## Histamine and neurogenic inflammation in the bladder

Interstitial cystitis (IC) and painful bladder syndrome (PBS) are both causes of neurogenic inflammation; in fact, an increased density of nerve fibres has been reported in these conditions (Peeker *et al.*, 2000). Evidence from both rodent and humans suggest that mast cells play an important role in these conditions. It has been shown that activated mast cells are associated with rodent neurogenic cystitis induced by the Bartha strain of pseudorabies virus (PRV) (Chen *et al.*, 2006; Jasmin *et al.*, 2000). Moreover, clinical studies have demonstrated an elevated number of mast cells in the lamina propria of IC bladder biopsies (Leiby *et al.*, 2007) and increased urinary histamine metabolites (el-Mansoury *et al.*, 1994). Although the central role of mast cells in PBS/IC is still unclear, results obtained in an *in vivo* model of IC pathogenesis suggest the existence of a positive feedback loop with SP containing peripheral nerves and mast cells: activation of the bladder-associated circuits in the CNS initiates SP release by peripheral nerves in the bladder, leading to SP-mediated mast cell activation. Consequently, mast cell degranulation induces bladder inflammation by acting on urothelium. Histamine contributes to the symptoms of IC/PBS, not only by evoking an inflammatory response, but is also associated with the pelvic pain. In fact, pain responses mediated by histamine and histamine receptors have been described in both animal and human models (Thilagarajah *et al.*, 2001; Mobarakeh *et al.*, 2006). Although the specific cell type (it could be mast cells, basophils, neutrophils or dendritic cells) or histaminergic neurons regulating histamine-mediated pain have not been identified, it has been demonstrated, using a model of PRV-induced pelvic pain in mast cell-deficient Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup> mice, that mast cells are required for histamine-mediated pelvic pain (Rudick *et al.*, 2008). However, the same authors demonstrated that Kit<sup>W-sh</sup>/Kit<sup>W-sh</sup> mice reconstituted with HDC<sup>-/-</sup> bone marrow exhibited diminished pain, thus suggesting that non-mast cell sources of histamine may also contribute to this pain response. Moreover, Rudick *et al.* (2008) demonstrated that PRV-induced pelvic pain is not dependent on TNF-mediated effects but is mediated by mast cell hista-

**Table 1**

Effect of selective histamine receptor antagonists on neurogenic inflammation

Effect	Histamine receptor subtype			
	H <sub>1</sub> R	H <sub>2</sub> R	H <sub>3</sub> R	H <sub>4</sub> R
Pain	↓	↓	↓	↓
Hyperalgesia <sup>a</sup>	↓	↓	↓	↓
Allodynia	?	?	↓	?
Itch	↓	↔	↑	↓
Sneezing response	↓ <sup>b</sup>	?	?	?

<sup>a</sup>The differential involvement of histamine receptor subtypes has been demonstrated in different experimental models.

<sup>b</sup>Only at high doses.

mine, which then induces pain by stimulating histamine H<sub>1</sub> and H<sub>2</sub> receptors. Thus, it has been suggested that antagonists of histamine H<sub>1</sub> and H<sub>2</sub> receptors are suitable candidates in clinical trials for the treatment of chronic pain conditions, such as IC-related pelvic pain. Indeed, the findings from pilot clinical studies suggest that antihistamine therapy could be effective in IC-related pelvic pain. In particular, a symptomatic improvement has been reported in 30% of patients treated with the H<sub>1</sub> receptor antagonist hydroxyzine hydrochloride at doses ranging from 25 mg day<sup>-1</sup> at night to 50 mg at night +25 mg in the morning over a 2 week period (Theoharides *et al.*, 1997). Although these positive results suggest a therapeutic role for histamine H<sub>1</sub> receptor antagonists in the treatment of IC/PBS, further studies with the newer generation of histamine H<sub>1</sub> receptor antagonists, which have fewer sedative effects, need to be conducted. Moreover, in a limited trial of PBS patients, the histamine H<sub>2</sub> receptor antagonist cimetidine produced significant improvements in the pain and nocturia associated with this condition (Thilagarajah *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 influenced by fluctuations in hormone levels. In fact, oestrogen receptors (ERs) are expressed on human mast cells and can induce them to degranulate, an effect inhibited by the ER antagonist tamoxifen (Rudick *et al.*, 2012).

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

## Conclusion

In conclusion, the experimental data described in this review generally show that histamine plays a key role in the complex physiopathological mechanism known as neurogenic inflammation (Table 1). We have summarized recent findings on the

role of histamine and the contribution of its four receptors, identified so far, to this condition, with particular focus on nociceptive pain, neurogenic inflammation in the skin, airways and interstitial cystitis. The experimental evidence, although not conclusive, indicates that several of the newly available histamine ligands have potential for clinical development as treatments for the pain and other symptoms associated with neurogenic inflammation.

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## Conflict of interest

The authors declared that they have no conflict of interest.

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