

Histamine, histamine receptors, and neuropathic pain relief

Ilona Obara^{1,2}  | Vsevolod Telezhkin³ | Ibrahim Alrashdi² | Paul L. Chazot⁴

¹School of Pharmacy, Newcastle University, Newcastle upon Tyne, UK

²Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

³School of Dental Sciences, Newcastle University, Newcastle upon Tyne, UK

⁴Department of Biosciences, Durham University, Durham, UK

Correspondence

Ilona Obara, School of Pharmacy, The Faculty of Medical Sciences, Newcastle University, King George VI Building, Newcastle upon Tyne NE1 7RU, UK.

Email: ilona.obara@ncl.ac.uk

Histamine, acting via distinct histamine H₁, H₂, H₃, and H₄ receptors, regulates various physiological and pathological processes, including pain. In the last two decades, there has been a particular increase in evidence to support the involvement of H₃ receptor and H₄ receptor in the modulation of neuropathic pain, which remains challenging in terms of management. However, recent data show contrasting effects on neuropathic pain due to multiple factors that determine the pharmacological responses of histamine receptors and their underlying signal transduction properties (e.g., localization on either the presynaptic or postsynaptic neuronal membranes). This review summarizes the most recent findings on the role of histamine and the effects mediated by the four histamine receptors in response to the various stimuli associated with and promoting neuropathic pain. We particularly focus on mechanisms underlying histamine-mediated analgesia, as we aim to clarify the analgesic potential of histamine receptor ligands in neuropathic pain.

1 | NEUROPATHIC PAIN AND ITS TREATMENT

Neuropathic pain was first defined by the International Association for the Study of Pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (Merskey & Bogduk, 1994). Fourteen years later, Treede et al. (2008) revised this definition and redefined it as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.” In the revised definition of neuropathic pain, two terms have received particular attention. First, the term “disease” which refers to all types of abnormal conditions including inflammation, autoimmune syndromes, and ion channel disorders (channelopathies) replaced the term “dysfunction.” Second, to avoid misdiagnosis of neuropathic pain as another type of pain originating from the nervous system, such as spasticity and rigidity of the muscles and bone (e.g., musculoskeletal pain), the term “nervous system” was replaced by the term “somatosensory system” (Finnerup et al., 2016). This revised definition of neuropathic pain describes

the nature of this condition more precisely and is, therefore, now widely accepted and approved by the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain. Neuropathic pain can be divided into two subtypes, peripheral or central, based on the anatomical location of the lesion or the disease, within the peripheral nervous system (PNS) or central nervous system (CNS), respectively.

It is estimated that the worldwide prevalence rate of neuropathic pain in the general population lies between 7% and 10%; however, this figure differs for different countries (van Hecke, Austin, Khan, Smith, & Torrance, 2014). The highest prevalence rates for neuropathic pain were recorded in Canada (17.9%) and in the United States (9.8–12.4%; VanDenKerkhof et al., 2016; Yawn et al., 2009), while a relatively low prevalence rate was noted in Austria and Netherlands (3.3% and 1%, respectively; Bouhassira, Lanteri-Minet, Attal, Laurent, & Touboul, 2008; Gustorff et al., 2008; Harifi et al., 2013). In the United Kingdom, France, and Brazil, it is reported that 7–10% of chronic pain sufferers have been affected by neuropathic pain (Fayaz,

Abbreviations: CaM, calmodulin; DRG, dorsal root ganglion; GSK3 β , glycogen synthase kinase 3 β ; IP₃, inositol triphosphate; KO, knockout; LC, locus coeruleus; PIP₂, phosphatidylinositol 4,5-bisphosphate; PNS, peripheral nervous system; SP, substance P

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Croft, Langford, Donaldson, & Jones, 2016). As a consequence of extended life expectancy, it is predicted that the worldwide prevalence rate of neuropathic pain is likely to increase further, because this type of chronic pain occurs with many common age-related diseases. Neuropathic pain is triggered by a lesion within the somatosensory system, trauma, or to toxic effects of certain medications (Colloca et al., 2017; Yu et al., 2013). Pathological conditions that are responsible for the development of neuropathic pain through injury include metabolic diseases (e.g., diabetic neuropathy), infection (e.g., postherpetic neuralgia), vascular disease (e.g., stroke), trauma (e.g., orofacial neuropathy), and cancer (Campbell & Meyer, 2006). Neuropathic pain is a complex condition that can either be constant or periodic and presents with a range of different symptoms. These symptoms can increase throughout the day with clinically relevant morning–evening differences and can be affected by gender and underlying aetiology (Gilon, Bailey, & Vandenkerkhof, 2013). Sufferers of neuropathic pain have ongoing, spontaneous pain that has a significant negative impact on quality of life and daily functioning, including physical, emotional, and social well-being (Jensen, Chodroff, & Dworkin, 2007).

The mechanisms underlying neuropathic pain are complex and multidimensional. Numerous pathophysiological and biochemical changes cause morphological and functional adaptations in the nervous system, including an increase in excitatory neurotransmitters and neuropeptides, for example, **histamine**, **bradykinin**, 5-HT, and glutamate, which leads to hyperexcitability (Baron, Binder, & Wasner, 2010). Likewise, injured peripheral nerve fibres give rise to an intense and prolonged input of ectopic activity to the CNS and may induce secondary changes to the excitability of the spinal cord dorsal horn neurons (Colloca et al., 2017; Ossipov & Porreca, 2005). These morphological changes and functional adaptations lead to abnormal sensory signs in patients with neuropathic pain presented as, for example, allodynia (pain due to a stimulus that does not normally activate the nociceptive system), hyperalgesia (an increased response to a stimulus that is normally painful), or sensory loss (hypoesthesia). Clinically, neuropathic pain manifests as evoked pain and presents in many ways such as burning, tingling, prickling, shooting, electric shock-like, jabbing, squeezing, spasm, or cold (Rice, Finnerup, Kemp, Currie, & Baron, 2018).

Animal models of neuropathic pain are essential in understanding the plethora of mechanisms that may drive neuropathic pain, allowing the field to identify potential therapeutic targets for the effective management of this condition. Extensive research in the pain field has developed and characterized a wide variety of animal models of neuropathic pain. The four most commonly used models, also adopted in some studies discussed in this review, are chronic constriction injury (Bennett & Xie, 1988), partial sciatic ligation (Seltzer, Dubner, & Shir, 1990), spinal nerve ligation (Kim & Chung, 1992), and spared nerve injury (Decosterd & Woolf, 2000) models. These models aim to simulate some of the clinical features of neuropathic pain, in the preclinical setting (e.g., allodynia and hyperalgesia), because a large proportion of peripheral neuropathic pain models, which are currently used in research, share alterations in hind-limb cutaneous sensory thresholds

following partial injury of a peripheral (usually sciatic) nerve. This is associated with the development of neuropathic pain symptoms, such as hyperalgesia and allodynia (Ma et al., 2003; Wall et al., 1979). There are also limitations associated with the use of animal models of neuropathic pain. These limitations are linked to challenges associated with (a) reliable and objective measures of behavioural responses to noxious stimuli, since animals cannot self-report and the experimenter can be biased, (b) appropriateness of the outcome measures, for example, sleep disturbance to reflect spontaneous pain, and (c) complexity of mechanisms underlying the development of neuropathic pain and their relevance to humans (Colleoni & Sacerdote, 2010).

Despite advances in the understanding of the underlying causes and mechanisms leading to the development and maintenance of neuropathic pain, 40% of Europeans who suffer from chronic pain did not achieve satisfactory pain control (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006), and to date, no medication has shown long-term efficacy and tolerability for neuropathic pain conditions. A significant contributing factor to these limited therapeutic strategies is that neuropathic pain has different aetiology and pathophysiology to any other type of chronic pain, making the management of this type of chronic pain particularly difficult and challenging (Finnerup et al., 2015). Consequently, there is a pressing need for the identification of new therapeutic strategies to improve management of neuropathic pain that will directly improve the outcome for pain sufferers.

The histamine system has been a target for multiple therapeutic interventions. Recently, growing evidence has supported the use of selective ligands of histamine **H₃ receptor** and **H₄ receptor** for the treatment of neuropathic pain (Bhowmik, Khanam, & Vohora, 2012; Chaumette et al., 2018; Popiolek-Barczyk et al., 2018; Sanna, Mello, Masini, & Galeotti, 2018). Approval in the European Union for the use of **pitolisant** (Wakix™), an antagonist/inverse agonist of H₃ receptors for the treatment of narcolepsy (Kollb-Sielecka et al., 2017), presents an opportunity to explore its clinical use for other conditions. Consequently, it seems an appropriate time to reconsider the histamine system as a therapeutic target for the management of neuropathic pain. This review aims to summarize the most recent findings on the role of histamine and its effects, mediated by different subtypes of histamine receptors, on neuropathic pain, with particular regard to the mechanisms underlying histamine-mediated analgesia.

2 | HISTAMINE, HISTAMINE RECEPTORS, AND PAIN

2.1 | Histamine and pain

Histamine (2-(4-imidazolyl)-ethylamine), one of the most extensively studied amino acid-derived neurotransmitters in the CNS and PNS, is involved in various physiological and pathological processes, including sleep-waking cycle, homeostasis, synaptic plasticity, and learning (Panula et al., 2015; Parsons & Ganellin, 2006; Pini, Obara, Battell, Chazot, & Rosa, 2016). Histamine is synthesized from the amino acid

L-histidine through oxidative decarboxylation via catalysis with the histidine decarboxylase enzyme (Bodmer, Imark, & Kneubuhl, 1999; Haas, Sergeeva, & Selbach, 2008) and is arguably the most pleiotropic molecule in the human and animal body, being present in many cell types (Lindskog, 2017). Histamine is released by neuronal and non-neuronal sources and is responsible for many physiological processes, including the contraction of smooth muscles of the lungs, uterus, and intestine, secretion of gastric acid in the stomach, and vasodilation, and modulation of heart rate and contractility (Parsons & Ganellin, 2006). Histamine also functions as a neurotransmitter, within the nervous system, regulating a variety of body functions, such as temperature control, memory, wakefulness, and pain sensation (Panula & Nuutinen, 2013).

Histamine is a key mediator in the processing of nociceptive information, acting in an antinociceptive manner in the CNS while, conversely, in a nociceptive manner in the PNS (Khalilzadeh, Azarpey, Hazrati, & Vafaei Saiah, 2018). In the PNS, histamine is released in response to tissue injury/damage, and, through the sensitization of polymodal nociceptors resulting in increased firing rates, it contributes to the generation of pain hypersensitivity. In neuropathic pain, histamine released in the periphery by mast cells has been shown to play an important role in the development of hypersensitivity following nerve injury. This pathological process is associated with recruitment of macrophages and neutrophils, and as histamine is a powerful chemoattractant of mast cells, it regulates this recruitment (Smith, Haskelberg, Tracey, & Moalem-Taylor, 2007; Zuo, Perkins, Tracey, & Geczy, 2003). Interestingly, it was also observed that peripherally acting histamine could interact with mechanisms underlying pruritus (itch) and pain. Findings suggest that low concentrations of histamine, acting on sensory neurons, produce pruritus with a high concentration leading to pain (Baron, Schwarz, Kleinert, Schattschneider, & Wasner, 2001; Hough & Rice, 2011; LaMotte, Simone, Baumann, Shain, & Alreja, 1987; Parsons & Ganellin, 2006; Pini et al., 2016; Simone, Alreja, & LaMotte, 1991). There is also evidence to show that histamine-induced itch can convert into pain associated with neuropathic hyperalgesia (Baron et al., 2001). Indeed, multiple itch pathways were identified indicating the presence of distinct itch-generating types of neuron, one responsible for transmitting itch sensation and the other, ultimately, for transmitting pain (Usoskin et al., 2015). In contrast to histamine activity in PNS, multiple behavioural studies have shown that histamine injected directly into the various brain areas (e.g., somatosensory cortex or hippocampus) attenuated pain (Erfanparast, Tamaddonfard, Farshid, & Khalilzadeh, 2010; Tamaddonfard & Hamzeh-Gooshchi, 2014).

Histamine exerts its effects via four distinct GPCR subtypes: **H₁**, **H₂**, **H₃**, and **H₄** receptors. These receptors differ in their pharmacology and signal transduction properties (Panula et al., 2015; Parsons & Ganellin, 2006; Simons & Simons, 2011). Thus, histamine has differential effects on neuropathic pain dependent upon the histamine receptor subtype it is bound to. As mentioned previously, this review aims to summarize histamine-mediated effects on neuropathic pain. Therefore, the next sections of this review focus on mechanisms underlying histamine-mediated analgesia.

2.2 | Histamine receptors and pain

Excitatory histamine receptor signalling in nociceptive pathways is associated with increased pain symptoms (Gangadharan & Kuner, 2013; Mobarakeh et al., 2000), whereas inhibition of histamine receptor signalling predominantly causes neuroprotective and antinociceptive effects (Bhowmik et al., 2012; Chazot & Care, 2005; Popiolek-Barczyk et al., 2018). Different subtypes of histamine receptors are expressed in both presynaptic and postsynaptic neuronal membranes (Brown, Stevens, & Haas, 2001; Parsons & Ganellin, 2006; Zhang et al., 2013). Presynaptic histamine receptors function as autoreceptors or heteroreceptors providing either positive or negative feedback regulation of neurotransmitter release from the axon terminals into the synaptic cleft (Nieto-Alamilla, Marquez-Gomez, Garcia-Galvez, Morales-Figueroa, & Arias-Montano, 2016). It could be concluded that the resultant excitatory or inhibitory physiological effect of histamine receptors depends on the action of the neurotransmitter and the subsequent downstream cascade.

Specificity of localization of histamine receptors in different parts of the nervous system, on either presynaptic or postsynaptic membranes, is determined by their physiological relevance (Parsons & Ganellin, 2006). Among the four subtypes of histamine receptors, **H₁** and **H₂** receptors are predominantly identified postsynaptically (Brown et al., 2001; Connelly et al., 2009; Zhang et al., 2013), with the location of the **H₄** receptor requiring further investigation (Connelly et al., 2009). Cross-desensitization and agonist-induced heterodimerization of **H₁** and **H₂** receptors (Alonso et al., 2013) may suggest a possible partnership between histamine receptors. Expression of **H₃** receptors was initially reported as exclusively presynaptic in the rat cerebral cortex (Arrang, Garbarg, & Schwartz, 1983; Clark & Hill, 1996), while postsynaptic expression of **H₃** receptors could not be completely excluded (Nieto-Alamilla et al., 2016). **H₃** receptors are predominantly expressed in neurons and, together with **H₄** receptors, have higher affinity (nM range) for histamine than **H₁** and **H₂** receptors (μ M range; Parsons & Ganellin, 2006). Expression of **H₃** and **H₄** receptors on the opposite sides of the synaptic cleft may contribute to their effects in neuropathic pain, although the neuronal topology of the **H₄** receptor still remains controversial. The use of selective ligands for histamine receptors has led to a better understanding of the physiological and pathophysiological roles of these receptors. The next section summarizes the effects produced by histamine receptor ligands on neuropathic pain.

Besides their presynaptic or postsynaptic localization, the physiological effects of histamine receptors are, to a great extent, determined by the type of guanine nucleotide-binding proteins (G-proteins) to which they are coupled (Leung & Wong, 2017). The difference in underlying signalling pathways may directly determine the effect on pain perception produced by selective ligands, even when they act at the same histamine receptor, as described below.

2.2.1 | **H₁** receptor

H₁ receptors are excitatory receptors, which couple with **G_q**-type proteins, leading to downstream activation of **PLC** and hydrolysis of

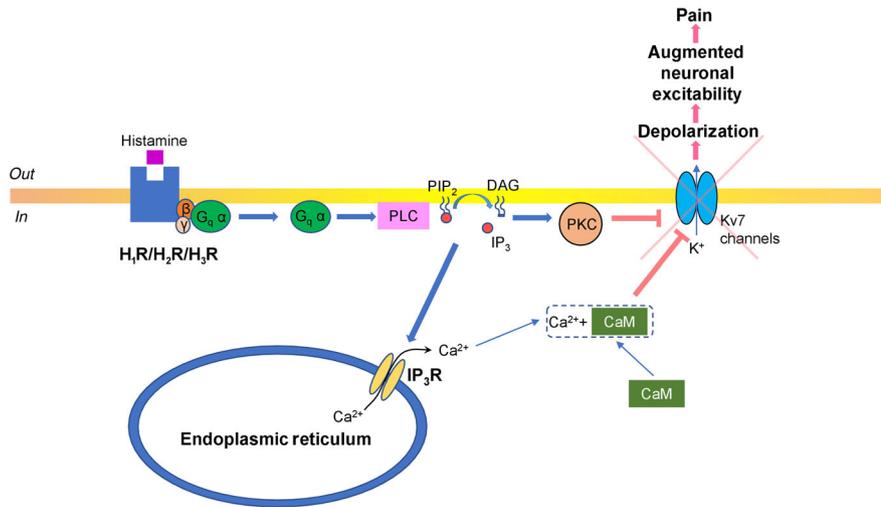


FIGURE 1 Diagram illustrating histamine receptor signalling—G_q pathway. Histamine binds to histamine receptors (H₁, H₂, or H₃ receptor subtypes) that are coupled with the G_q-type protein. G_q α subunit activates PLC which hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP₂), subsequently producing DAG, that remains in the inner leaflet of the plasma membrane activating PKC, and water soluble inositol triphosphate (IP₃), which binds to **inositol triphosphate sensitive receptor** (IP₃R) and stimulates Ca²⁺ release from endoplasmic reticulum. This intracellular Ca²⁺ forms a complex with calmodulin (CaM) Ca²⁺/CaM and induces PKC-dependent phosphorylation. This suppresses the activity of potassium voltage-gated channels type 7 (K_v7 channels), which depolarizes the neurons, and leads to the augmentation of neuronal excitability, which manifests as increased pain symptoms

phosphatidylinositol 4,5-bisphosphate (PIP₂) to produce DAG and **inositol triphosphate** (IP₃). DAG subsequently activates PKC at the membrane, while IP₃ diffuses and binds to IP₃ receptors on the endoplasmic reticulum to mobilize stored calcium (Ca²⁺). These changes cause PIP₂ depletion and increased intracellular concentration of Ca²⁺. This increased concentration of Ca²⁺ activates PKC-dependent phosphorylation and forms a complex with **calmodulin** (Ca²⁺/CaM), both of which suppress **potassium voltage-gated type 7 (Kv7) channels** (Figure 1), leading to depolarization and increased nociception (Brown & Passmore, 2009; Chen, Li, Hielt, & Obukhov, 2016).

2.2.2 | H₂ receptor

H₂ receptors are postsynaptic, predominantly associated with AC via coupling to G_s and, in a similar fashion to H₁ and H₃ receptors, G_q proteins, both pathways initiating excitatory downstream signalling. Thus, H₂ receptor inhibition yielded efficient antinociceptive effects

(Mojtahedin, 2016). G_s α subunit stimulates AC with consequent augmented production of cAMP and consequent activation of **PKA** (Brown et al., 2001). Elevated cAMP concentration up-regulates PKA, which as reported for hippocampal neurons, could activate ligand gated **α-AMPA receptors** with resultant depolarization and increase of neuronal firing (Park et al., 2016). Also, as it was reported for after-hyperpolarization in enteric neurons, PKA inhibits small conductance **Ca²⁺-activated potassium (KCa) channels** with resultant augmented neuronal excitability (Figure 2; Vogalis, Harvey, & Furness, 2003).

2.2.3 | H₃ receptor

Presynaptic H₃ receptors are coupled with G_i (AC inhibitory) proteins (Nieto-Alamilla et al., 2016; Schlicker & Kathmann, 2017). G_i α subunit-mediated AC inhibition results in a decreased intracellular concentration of cAMP and subsequent down-regulation of PKA (Nieto-Alamilla et al., 2016). In sympathetic and sensory neurons, it

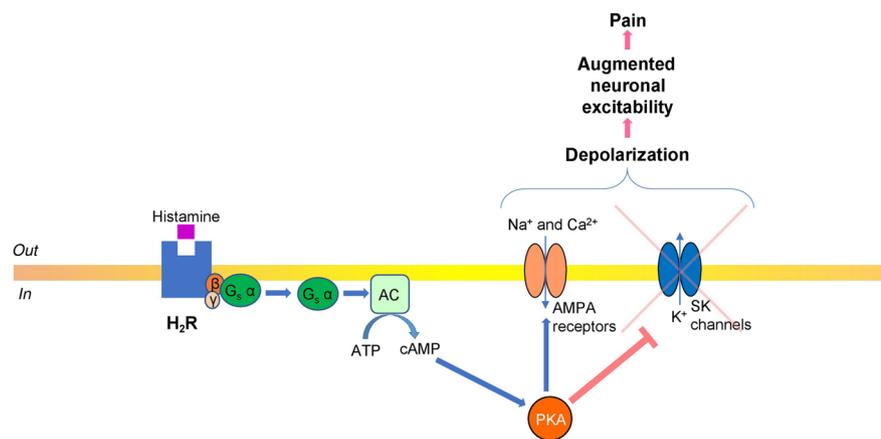


FIGURE 2 Diagram illustrating histamine receptor signalling—G_s pathway. Histamine binds to the H₂ receptor subtype that is coupled with the G_s-type protein. G_s α subunit activates AC, with subsequent production of cAMP, which then stimulates PKA. PKA-dependent phosphorylation activates ligand gated α-AMPA receptors, which open and facilitate influx of Na⁺ and, less commonly, Ca²⁺. PKA also suppresses K⁺ efflux through small conductance Ca²⁺-activated potassium channels (SK channels). Both the activation of AMPA receptors and inhibition of SK channels depolarize the neurons, with consequent augmentation of their excitability and increased pain signalling

was reported that H₃ receptor activation stimulated dissociation of G_i β and γ subunits from G_i α subunit, which then inhibited voltage-gated Ca²⁺ influx through N-, P-, and Q-type Ca²⁺ channels (Zamponi & Currie, 2013), and stimulated **G protein-coupled inwardly rectifying potassium (Kir) channels** (Luscher & Slesinger, 2010). Both mechanisms could hyperpolarize presynaptic neurons, reduce neuronal excitability, and produce pain relief (Figure 3).

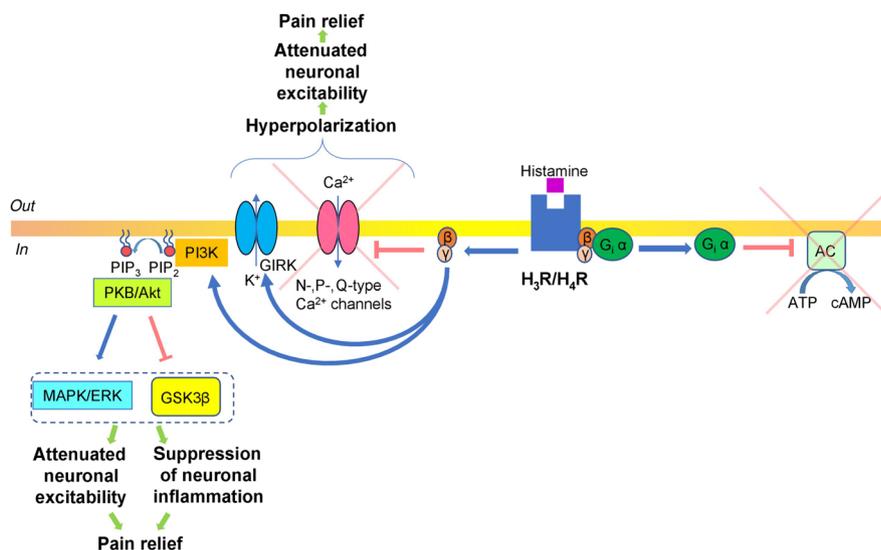
Besides the G_i pathway, postsynaptic activation of H₃ receptors was reported to stimulate PLC in a subpopulation of striatal neurons, with subsequent activation of the IP₃ pathway followed by increased intracellular concentrations of Ca²⁺ (Rivera-Ramírez et al., 2016). Thus, it is analogous to the mechanisms described for H₁ /H₂ receptors coupled to G_q proteins (Figure 1). Similarly, the H₁ and H₂ receptor G_q cascade PLC signalling pathways modulate neuronal excitability with resultant potential facilitation of pain sensitivity. Furthermore, H₃ receptor activation was established to inhibit **glycogen synthase kinase 3β** (GSK3β) and MAPK/ERK pathways (Bongers et al., 2007; Morita, Aida, & Miyamoto, 1983). These effects are translated via G_i β and γ subunits (Lai et al., 2016), which up-regulate the **PI3K** pathway with subsequent production of **phosphatidylinositol 3,4,5-triphosphate** (PIP₃) from PIP₂, which results in the recruitment of **PKB** (Akt). PKB is initially activated by **phosphoinositide-dependent kinase 1** (PDK1) and **mammalian target of rapamycin** complex 2-

dependent phosphorylation (Dzambo, Zhou, Huang, & Halliday, 2014). PKB, via phosphorylation, inactivates GSK3β, which decreases neuronal excitability (Paul et al., 2016), inhibits neuronal inflammation (Maixner & Weng, 2013), and, subsequently, relieves pain. PKB-dependent phosphorylation that activates the MAPK/ERK cascade was also reported to be a highly efficient neuroprotective mechanism for chronic inflammatory and neuropathic pain (Cruz & Cruz, 2007; Figure 3).

2.2.4 | H₄ receptor

The role of H₄ receptors in the nervous system is poorly understood (Schneider & Seifert, 2016). H₄ receptors are known to be coupled to G_i proteins, and their downstream pathways are postulated to be similar to those described for H₃ receptors (Figure 3). Compared to the other three types of histamine receptors, the H₄ receptor is not expressed abundantly in the CNS and PNS. By quantitative single-cell Ca²⁺ imaging, it was demonstrated that histamine induces a Ca²⁺ increase in a subset of sensory neurons (3–10%) via activation of the H₁ and H₄ receptors as well as inhibition of the H₃ receptor. It is assumed that the decreased threshold in response to H₃ receptor antagonism, which accounts for the analgesic effect of H₃ receptor antagonists, activates H₁ and H₄ receptors on sensory neurons, which

FIGURE 3 Diagram illustrating histamine receptor signalling—G_i pathway. Histamine binds to the histamine receptors (presynaptic and postsynaptic H₃ or H₄ receptor subtypes) that are coupled with G_i-type protein. The G_i α subunit inhibits AC with subsequent suppression of cAMP production and inhibition of PKA activity. Also, G_i β and γ subunits can inhibit Ca²⁺ influx through voltage-gated N-, P-, and Q-type Ca²⁺ channels and stimulate G protein-coupled inwardly rectifying potassium (GIRK) channels, with resultant K⁺ efflux. Both effects on N-type Ca²⁺ and GIRK channels result in the development of hyperpolarization, attenuation of neuronal excitability, and resultant pain relief. Besides G_i α subunit effects, H₃ receptor activation could produce analgesic effects through G_i β and γ subunits, which up-regulate the PI3K pathway, with the subsequent production of phosphatidylinositol 2,4,5-trisphosphate (PIP₃) from phosphatidylinositol 4,5-bisphosphate (PIP₂). PIP₃ recruits PKB (Akt), which phosphorylates and inactivates glycogen synthase kinase 3β (GSK3β). In parallel, PKB (Akt)-dependent phosphorylation additionally activates the MAPK/ERK cascade. The action on both GSK3β and MAPK/ERK decreases neuronal excitability, inhibits mechanisms of neuronal inflammation, and, therefore, produces pain relief



in turn results in the excitation of histamine-sensitive afferents and, therefore, may result in a modulation of pain sensitivity (Rossbach et al., 2011).

3 | HISTAMINE RECEPTOR LIGANDS AND NEUROPATHIC PAIN

3.1 | H₁ and H₂ receptor ligands and neuropathic pain

The best-known roles for the H₁ receptor are regulation of vasodilation and bronchoconstriction on multiple cell types, including endothelial and smooth muscle cells, while the H₂ receptor is primarily involved in the modulation of gastric secretion on parietal cells (Barocelli & Ballabeni, 2003; Simons, 2003). There is also evidence for their expression in the nervous system, where they regulate some neuronal functions (Haas et al., 2008; Kashiba, Fukui, & Senba, 2001; Murakami et al., 1999).

Both H₁ and H₂ receptors have been implicated in the role of histamine in nociception and chronic pain (Table 1). Interestingly, with the discovery of H₁ and H₂ receptor ligands in the 1950s, controlled clinical studies using these H₁ and H₂ receptor antagonists reported mild analgesic activity and their potential as analgesic adjuvants, particularly in conditions where pain was induced by histamine. Most of the clinical studies focused on **diphenhydramine** (first generation H₁ receptor antagonist) and showed its analgesic potential in the treatment of dysmenorrhea, atypical head and face pain, trigeminal neuralgia, and thalamic syndrome (Rumore & Schlichting, 1986). In addition, diphenhydramine, when combined with opioids, showed its potential as an analgesic adjuvant in refractory cancer pain (Santiago-Palma, Fischberg, Kornick, Khjainova, & Gonzales, 2001). In addition to clinical evidence for the analgesic potential of H₁ and H₂ receptor antagonists, preclinical studies identified the expression of H₁ and H₂ receptors in nociceptive pathways and, therefore, further supported the roles of H₁ and H₂ receptors in the regulation of pain. There are limited anatomical data available for H₂ receptors, despite the report of H₂ receptor mRNA expression in human spinal cord (Murakami et al., 1999). The potential involvement of H₁ receptors in the modulation of neuropathic pain has been investigated more extensively. In studies using in situ hybridization techniques in the guinea pig, the H₁ receptor mRNA was shown to be expressed in about 15–20% of the central trigeminal and lumbar dorsal root ganglion (DRG) neurons. These sensory neurons are fundamental to nociceptive processes, potentially responding to histamine by acting on H₁ receptors. These neurons are exclusively small in size and coexpress isolectin B4, but not **substance P** (SP) or **CGRP**, suggesting characteristics of unmyelinated C-fibres involved in acute nociception. Interestingly, the potential role of H₁ receptors in the regulation of neuropathic pain sensitivity can be explained by the marked (up to fourfold) increase in H₁ receptor expression in the mainly small-sized DRG neurons, 1–5 days after a crush injury of the sciatic nerve. Moreover, this study showed new characteristics of peptidergic (SP/CGRP) sensory neurons not

detected prior to nerve injury, suggesting that the sensory modalities evoked by histamine acting via H₁ receptors in normal and neuropathic pain states may result in different effects. This demonstration of the potential up-regulation of H₁ receptor number in injured afferent nerves further supports the involvement of H₁ receptors in the regulation of neuropathic pain hypersensitivity, presumably expressed on unmyelinated C-fibres (Kashiba et al., 2001). The earliest electrophysiological study to probe the histaminergic system in neuropathic pain transmission reported that daily injections of **astemizole**, a CNS-sparing H₁ receptor antagonist, acting via peripheral histamine-sensitive C-fibres, blocked ectopic spontaneous discharges from the neuroma and suppressed autotomy following sciatic and saphenous neurectomy (Seltzer et al., 1991; Yu et al., 2013). More recently, i.c.v. injection of histamine blocked mechanical and thermal hypersensitivity associated with neuropathic pain (Sanna et al., 2015; Wei et al., 2016). However, these pain-modulatory effects of histamine can vary depending on the dose of histamine administered i.c.v., due to an action on H₂ receptors and the involvement of adrenoceptors (Wei et al., 2014; Wei et al., 2016).

To further support the role of H₁ and H₂ receptors in the regulation of pain, separate studies using knockout (KO) mice lacking H₁ and H₂ receptors demonstrated that these mice displayed significantly lower responses to nociceptive stimuli when compared to their wild-type controls (Mobarakeh et al., 2002; Mobarakeh, Takahashi, Sakurada, Kuramasu, & Yanai, 2006). Interestingly, the antinociceptive phenotype of H₂ receptor KO mice was relatively less prominent when compared to H₁ receptor KO mice, suggesting a potentially distinct role for these receptors in the modulation of pain. Indeed, behavioural studies using a model of neuropathic pain, induced by the partial ligation of the sciatic nerve, showed that the CNS-permeable H₁ receptor antagonist **mepyramine**, but not the H₂ receptor CNS-sparing antagonist **cimetidine**, blocked the effects of histidine on neuropathic pain hypersensitivity and spinal microglia activity (Yu et al., 2016). In addition, Jaggi et al. (2017) suggested that the H₁ receptor plays a more important role in a vincristine-induced model of neuropathic pain, when compared to H₂ receptors. However, Khalilzadeh et al. (2018) observed different behavioural effects upon tibial nerve transection-induced neuropathic pain with respect to the extent of brain penetration of the ligands, in a study focused on centrally active and centrally sparing H₁ and H₂ receptor antagonists. Specifically, both **chlorpheniramine**, a centrally and peripherally active H₁ receptor antagonist, and **fexofenadine**, an H₁ receptor, centrally sparing antagonist, were found to profoundly decrease the mechanical hypersensitivity associated with the development of neuropathic pain. In contrast, while **ranitidine**, a widely used centrally permeable H₂ receptor antagonist, also improved mechanical hypersensitivity, **famotidine**, a centrally sparing H₂ receptor antagonist, was ineffective. These results indicate that both blood brain barrier penetrating and poorly penetrating histamine H₁ receptor antagonists can block neuropathic pain hypersensitivity, but only the blood brain barrier penetrating histamine H₂ receptor antagonist can generate an analgesic effect in neuropathic pain. In line with this observation, histamine-induced mechanical hypersensitivity

TABLE 1 A summary of the effects produced by histamine receptor ligands in animal models of neuropathic pain

Drug	Model	Strain	Test	Effect	Reference
H₁ antagonists					
Astemizole	Neurectomy	Sabra rats	Score	i.p. suppressed autotomy	Seltzer, Paran, Eisen, & Ginzburg, 1991
Chlorpheniramine	TNT	Wistar rats	Acetone von Frey Double plate Open field	i.p. reduced allodynia and prevented cold plate avoidance behaviour	Khalilzadeh et al., 2018
	PLSN	Wistar rats	Hargreaves Randall-Selitto	i.p. suppressed and alleviated hyperalgesia	Zuo et al., 2003
Fexofenadine	TNT	Wistar rats	Acetone von Frey Double plate Open field	p.o. reduced allodynia and prevented cold plate avoidance behaviour	Khalilzadeh et al., 2018
Loratadine					
	Peripheral axotomy	Sprague-Dawley rats	Score of autotomy	i.p. did not block analgesic effects of histidine on pain behaviour but alone suppressed autotomy	Yu et al., 2013
Mepyramine (pyrilamine)	PLSN	Sprague-Dawley rats	von Frey IR laser	Intrathecal, i.c.v. blocked analgesic effects of histidine on pain behaviour	Yu et al., 2016
	SNL	Hannover-Wistar rats	von Frey Radiant heat	Intrathecal did not attenuate the antihyperalgesia effect of histamine	Wei, Viisanen, You, & Pertovaara, 2016
	SNL	Hannover-Wistar rats	von Frey test Radiant heat	Into LC did not attenuate the antihyperalgesia effect of histamine and alone failed to influence pain	Wei, Jin, Viisanen, You, & Pertovaara, 2014
	PLSN	Rats	von Frey	i.c.v. was ineffective	Huang, Adachi, Nagaro, Liu, & Arai, 2007
Promethazine					
	Vincristine induced	Wistar albino rats	Pinprick Acetone Hot plate	i.p. reduced hyperalgesia and allodynia	Jaggi, Kaur, Bali, & Singh, 2017
H₂R antagonists					
Cimetidine	PLSN	Sprague-Dawley rats	von Frey IR laser	Intrathecal, i.c.v. did not block histidine's analgesic effects on pain behaviour	Yu et al., 2016
	PLSN	Wistar rats	Hargreaves Randall-Selitto	i.p. suppressed and alleviated hyperalgesia	Zuo et al., 2003
Famotidine	TNT	Wistar rats	Acetone von Frey Double plate Open field	p.o. was ineffective in all tests	Khalilzadeh et al., 2018
	PLSN	Sprague-Dawley rats	von Frey Diode laser	i.p. reduced allodynia and hyperalgesia	Yue et al., 2014

(Continues)

TABLE 1 (Continued)

Drug	Model	Strain	Test	Effect	Reference
Ranitidine	TNT	Wistar rats	Acetone von Frey Double plate Open field Pinprick Acetone Hot plate von Frey	i.p. reduced allodynia and prevented cold plate avoidance behaviour	Khalilzadeh et al., 2018
	Vincristine induced	Wistar rats	Pinprick Acetone Hot plate von Frey	i.p. reduced hyperalgesia and allodynia	Jaggi et al., 2017
	PLSN	Rats	von Frey	i.c.v. increased hypersensitivity	Huang et al., 2007
Zolantidine	SNL	Hannover-Wistar rats	von Frey Radiant heat	i.t. attenuated the antihypersensitivity effect of histamine	Wei et al., 2016
	SNL	Hannover-Wistar rats	von Frey Radiant heat	Into LC attenuated histamine's analgesic effect but alone failed to influence pain	Wei et al., 2014
H ₃ R antagonists and H ₃ R antagonists/inverse agonist					
A-960656	SNL	Hannover-Wistar rats	von Frey Radiant heat	Into LC reduced hypersensitivity	Wei et al., 2014
	SNL	Hannover-Wistar rats	von Frey Radiant heat	i.t. reduced hypersensitivity	Wei et al., 2016
	SNL	Sprague-Dawley rats	von Frey	p.o. reduced hypersensitivity	Cowart et al., 2012
Ciproxifan	SNI	BL6 mice	Hargreaves Dynamic plantar aesthesiometer	i.p. was ineffective	Zhang et al., 2012
E-162	CCI	Swiss CD1 mice	von Frey Cold plate Tail-flick	i.p. reduced hypersensitivity	Popiolek-Barczyk et al., 2018
GSK189254	CCI	Random-hooded rats	von Frey Randall-Selitto	p.o. reduced allodynia and hyperalgesia	Medhurst et al., 2008
	SNL	Sprague-Dawley rats	von Frey	i.p. reduced allodynia	Hsieh et al., 2010
GSK334429	CCI	Random-hooded rats	von Frey Randall-Selitto	p.o. reduced allodynia and hyperalgesia	Medhurst et al., 2008
Pitolisant	SNI	BL6 mice	Hargreaves Dynamic plantar aesthesiometer	i.p. was ineffective, high doses increased thermal but not mechanical hypersensitivity	Zhang et al., 2012
S38093	CCI and oxaliplatin induced	Sprague-Dawley rats	Randall-Selitto Tail-immersion (10°C)	p.o. reduced hypersensitivity	Chaumette et al., 2018

(Continues)

TABLE 1 (Continued)

Drug	Model	Strain	Test	Effect	Reference
ST-889	SNI	BL6 mice	Hargreaves Dynamic plantar aesthesiometer	i.p. was ineffective	Zhang et al., 2012
Thioperamide	PLSN PLSN	Rats Sprague-Dawley rats	von Frey Randall-Selitto	i.c.v. increased but i.p. reduced hypersensitivity i.p. increased hypersensitivity	Huang et al., 2007 Smith et al., 2007
H ₄ R agonists					
ST-1006	SNI	CD1 mice	Hargreaves Dynamic plantar aesthesiometer	i.c.v. reduced allodynia and hyperalgesia	Sama et al., 2015
VUF-8430	SNI	CD1 mice	Hargreaves Dynamic plantar aesthesiometer	i.c.v. reduced allodynia and hyperalgesia	Sama et al., 2015
	SNI	CD1 mice	Hargreaves Dynamic plantar aesthesiometer	i.t. reduced allodynia and hyperalgesia	Sama, Lucarini, et al., 2017
	PLSN	Sprague-Dawley rats	Randall-Selitto	i.p. reduced hypersensitivity	Smith et al., 2007
H ₄ R antagonists					
JNJ777120	PLSN	Sprague-Dawley rats	Randall-Selitto	i.p. increased hypersensitivity	Smith et al., 2007
	SNL	Sprague-Dawley rats	von Frey	i.p. reduced allodynia	Hsieh et al., 2010
JNJ10191584	SNI	CD1 mice	Hargreaves Dynamic plantar aesthesiometer	p.o. blocked the analgesic effect of i.c.v. ST-1006 and VUF-8430 and was ineffective alone	Sama et al., 2015
	SNI	CD1 mice	Hargreaves Dynamic plantar aesthesiometer	p.o. blocked the analgesic effect of i.t. VUF-8430 and was ineffective alone	Sama et al., 2015
TR-7	CCI	Swiss CD1 mice	von Frey Cold plate Tail-flick	i.p. reduced hypersensitivity	Popiolek-Barczyk et al., 2018

Abbreviations: CCI, chronic constriction nerve injury; LC, locus coeruleus; PLSN, partial ligation of sciatic nerve; SNI, spared nerve injury; SNL, spinal nerve ligation; TNT, tibial nerve transection.

was prevented by spinal pretreatment with zolantidine, a brain penetrating H₂ receptor antagonist, as well as localized peripheral administration of cimetidine (H₂ receptor antagonist) and chlorpheniramine (H₁ receptor antagonist) into the plantar side of the hindpaw (Zuo et al., 2003).

Taken together, these results indicate that the brain histamine, acting particularly via central H₁ and H₂ receptors, may be involved in the modulation of neuropathic pain. These studies consistently support the idea that CNS-permeable H₁ and H₂ receptor antagonists may potentially be used as analgesics for patients with neuropathic pain. The involvement of central H₂ receptors in the regulation of neuropathic pain hypersensitivity was also demonstrated in studies where histamine (presumably postsynaptically- induced) facilitated mechanical hypersensitivity mediated by **NMDA** receptors as well as, in a dose-dependent manner, **Nav1.8** channel expression in primary afferent neurons in the sciatic nerve and L4/L5 DRG (Wei et al., 2016; Yue et al., 2014). While sodium channels are responsible for the development and maintenance of neuropathic pain (Ossipov & Porreca, 2005; Yue et al., 2014), the above studies highlight the importance of histamine acting via H₂ receptors in the regulation of mechanisms associated with neuropathic pain states. The influence of the H₂ receptor on non-neuronal cells (mast cells) is discussed later in this review.

3.2 | H₃ receptor ligands and neuropathic pain

H₃ receptors are mostly presynaptic, expressed as autoreceptors on histaminergic neurons involved in the negative feedback control of histamine levels (Arrang et al., 1983; Hough & Rice, 2011), while H₃ heteroreceptors on postsynaptic nonhistaminergic neurons also regulate negatively the release of neurotransmitters, such as **ACh**, **dopamine**, 5-HT, and **noradrenaline** (Blandina, Munari, Giannoni, Mariottini, & Passani, 2010; Gemkow et al., 2009; Giannoni et al., 2010). Since the cloning of H₃ receptors (Lovenberg et al., 1999), there has been an increased interest within the pharmaceutical industry in developing ligands for this receptor to target several diseases, including neuropathic pain. This interest was strongly fuelled by the report of H₃ receptor expression in nociceptive pathways, suggesting its functional involvement in the regulation of nociceptive transmission (Cannon et al., 2007). Indeed, the histamine H₃ receptor consists of several functional isoforms expressed in both the CNS and PNS, particularly along the ascending nociceptive pathway and descending pain-control pathway, that are critical for the processing of nociceptive information. Within the CNS, this receptor has been found in various brain areas, such as thalamus, hypothalamus, prefrontal cortex, and periaqueductal grey area (Drutel et al., 2001), and in the spinal cord (Cannon et al., 2007; Heron, Rouleau, Cochois, Pillot, & Schwartz, 2001; Medhurst et al., 2008). In the periphery, the expression of H₃ receptors has been identified in DRG, superior cervical ganglia, and dermal tissues (Cannon et al., 2007; Medhurst et al., 2008).

However, while the localization of H₃ receptors strongly suggests its functional involvement in the regulation of nociceptive transmission, pharmacological studies using agonists and antagonists of H₃

receptors are confusing as these drugs have different effects on the nociceptive threshold depending on the pain model used, the nociceptive stimulus selected, together with the affinity and selectivity for the histamine receptors, and the dose and routes of administration (Huang et al., 2007; Smith et al., 2007). Several studies have reported inhibitory effects on pain following activation of H₃ receptors using agonists (Cannon et al., 2003; Hasanein, 2011). The involvement of H₃ receptors in neuropathic pain has been implicated using a range of H₃ receptor antagonists/inverse agonists (Table 1). The antagonism at H₃ receptors results in reduced mechanical and cold hypersensitivity associated with neuropathic pain (chronic constriction injury model or spinal nerve ligation model) as shown in studies using E-162 or GSK189254, selective H₃ receptor antagonists, where its strong analgesic effect was observed after a single systemic (i.p.) dose (Hsieh et al., 2010; Popiolek-Barczyk et al., 2018). In addition, repeated, orally delivered doses of GSK189254, **GSK334429**, S38093, and A-960656, selective H₃ receptor antagonists/inverse agonists, significantly reduced paw withdrawal threshold to mechanical stimuli or elicited an analgesic effect in the vocalization test of neuropathic pain (chronic constriction injury model or spinal nerve ligation model), showing comparable efficacy to **pregabalin** or **gabapentin**, which are both used clinically as first-line treatments (Chaumette et al., 2018; Cowart et al., 2012; Medhurst et al., 2008). The analgesic efficacy of S38093 was also confirmed in other models of neuropathic pain with different aetiologies, such as diabetic and chemotherapeutic agent-induced neuropathy, where the drug again showed analgesic potency similar to pregabalin and gabapentin (Chaumette et al., 2018). Analgesia induced by the blockade of the H₃ receptor is possibly the result of the regulation of histamine levels in the CNS, as depolarization activates histamine synthesis in nerve endings, a process that is controlled by H₃ autoreceptors (Arrang et al., 1983; Hough & Rice, 2011). Indeed, Wei et al. (2016) proposed that blocking the autoinhibitory H₃ receptor on histaminergic terminals in the pontine locus coeruleus (LC), which receives efferent projections from the histaminergic tuberomammillary nucleus, facilitated endogenous release of histamine leading to neuropathic hypersensitivity inhibition through the regulation of descending noradrenergic pathways. In addition, there is accumulating evidence to support the idea that the analgesic effects of H₃ receptor antagonists/inverse agonists in neuropathic pain can be partially mediated by **α₂ adrenoceptor** desensitization (induced by H₃ receptor antagonists/inverse agonists) in the LC and spinal cord. This suggests an inhibitory role for the central heteroreceptor noradrenergic transmission in the efficacy of H₃ receptor antagonists/inverse agonists. In agreement with this idea, systemic administration of α₂ adrenoceptor agonists or nerve injury-induced activation of these α₂ adrenoceptors decreases the firing activity of LC noradrenergic cells, resulting in the dampening of noradrenaline release in the terminal area (e.g., prefrontal cortex or spinal cord) and promoting neuropathic hypersensitivity by attenuating descending inhibition (Chaumette et al., 2018; Wei et al., 2010; Wei et al., 2014). In contrast, treatment with H₃ receptor antagonists/inverse agonists restores LC and decreases α₂ adrenoceptor activity, respectively, potentially leading to relief in neuropathic pain hypersensitivity

(Chaumette et al., 2018; Wei et al., 2010). To further support this proposed mechanism, it was shown that bilateral lesion of the LC, transection of the spinal cord, or direct injection of a α_2 agonist (fadolmidine) into the LC reversed the antihyperalgesic effect produced by H_3 receptor antagonists, A-960656 or GSK189254 (Chaumette et al., 2018; McGaraughty, Chu, Cowart, & Brioni, 2012; Wei et al., 2014). In line with this, electrophysiological studies performed in anaesthetized animals indicated that, after systemic administration, GSK189254 dose-dependently decreased both evoked and spontaneous firing of wide dynamic range neurons in neuropathic, but not sham-operated rats (McGaraughty et al., 2012). However, analgesia induced by the blockade of the H_3 receptor can also be mediated via H_3 heteroreceptors that regulate other neurotransmitters' release; the blockade of the H_3 receptor is known to increase the release of ACh, dopamine, 5-HT, noradrenaline, and SP in the CNS (Blandina et al., 2010; Gemkow et al., 2009; Giannoni et al., 2010).

Interestingly, the majority of the behavioural observations published indicate that H_3 receptor antagonists/inverse agonists do not produce any antinociceptive effects in naïve rodents, suggesting a possibility that H_3 receptors are not involved or tonically activated in nociception (at least in relation to acute mechanical nociception), but are critical for pathological pain states, particularly for mechanical hypersensitivity (Chaumette et al., 2018; McGaraughty et al., 2012). Also, H_3 receptor KO mice showed unaltered response to mechanical pinch (Cannon et al., 2003), and multiple studies suggest modality (mechanical vs. heat) and intensity (preferential responses to low-intensity tail pinch stimulation; Cannon et al., 2003) with specific antinociceptive effects mediated by H_3 receptors. H_3 receptor antagonists/inverse agonists at a dose that produced a significant reduction of mechanical hypersensitivity in neuropathic pain did not attenuate heat hypersensitivity indicating that the antihyperalgesic effect was due to selective depression of spinal sensory rather than motor neurons (Wei et al., 2014; Wei et al., 2016). To support this, in situ hybridization studies revealed H_3 receptor mRNA transcripts in the sensory neurons of the dorsal horn and DRG (Heron et al., 2001). Moreover, receptor autoradiography studies, using [3 H] GSK189254, showed specific H_3 receptor binding sites in the dorsal horn of the spinal cord and DRG, confirming these as sites of action of H_3 receptor antagonists within structures receiving histaminergic innervation and are critical for processing of pain information (Medhurst et al., 2008). The modality- and intensity-specific antinociceptive effects of H_3 receptor activation/inhibition may also suggest involvement of a specific population of sensory fibres that regulate mechanical hypersensitivity. In line with this, immunohistochemical studies identified localization of H_3 receptors (confirmed by H_3 receptor KO mice) on medium-size cell bodies in DRG and on small-calibre periaxonal, peptidergic A δ fibres that ramified in dorsal horn laminae I, II, and V and coexpress immunoreactivity for acid-sensing ion channel 3 and 200-kD neurofilament protein. This strongly supports the involvement of H_3 receptors in the regulation of mechanical sensitivity (Cannon et al., 2007). In addition, Medhurst et al. (2007) showed that GSK207040 and GSK334429, selective H_3 receptor

antagonists, blocked the secondary mechanical allodynia in the capsaicin-induced model of pain. Secondary mechanical hypersensitivity is known to be exclusively signalled by A-fibres and amplified by sensitized dorsal horn neurons (Magerl, Fuchs, Meyer, & Treede, 2001; Treede & Magerl, 2000). Thus, presumably reducing the sensitivity of H_3 receptor-positive A-fibres with selective H_3 receptor antagonists resulted in a diminished input to the dorsal horn and the subsequent amplification of the A-fibres response, confirming the potential role for H_3 receptors in the modulation of central sensitization processes. In contrast, thermal (heat) hypersensitivity is generally regarded as a sign of the peripheral sensitization of C-fibres, which do not express H_3 receptors (Cannon et al., 2007; Gold & Gebhart, 2010). The only study that reported a significant increase in thermal (radiant heat in Hargreaves test), but not mechanical, threshold in the spared nerve injury model of neuropathic pain used the selective H_3 receptor inverse agonist pitolisant (Wakix™). The drug produced this unexpected effect at a dose 5 \times higher than its clinically relevant dose, and pharmacological analysis of this effect suggested at least partial involvement of transient receptor potential cation channel subfamily V member 1 (TRPV1), without any contribution of H_3 receptors (Zhang et al., 2012). Interestingly, the H_3 receptor antagonist/inverse agonist E-162, at a dose that produced a significant reduction in mechanical hypersensitivity, also attenuated the response to cold in neuropathic pain (Popielek-Barczyk et al., 2018). The signalling of cool temperatures that become aversive in neuropathic pain is known to be mediated via the TRPM8 receptor, a member of the TRP channel family (Knowlton et al., 2013). It was reported that the number of TRPM8-positive A δ -fibres (but not C-fibres) increases after nerve injury (Ji, Zhou, Kochukov, Westlund, & Carlton, 2007); thus, it is possible that H_3 receptor-positive A-fibres are probably sensitive to cooling and may contribute to cold hypersensitivity in neuropathic pain.

The most significant inconsistencies in behavioural outcomes in neuropathic pain can be found in studies on the role of a first-generation imidazole-based molecule, thioperamide (H_3 receptor antagonist, H_3 / H_4 receptor inverse agonist), in the regulation of mechanical hypersensitivity in neuropathic pain. On the one hand, blocking H_3 receptors (and H_4 receptors) by thioperamide resulted in a significant enhancement of mechanical hyperalgesia in a rat model of neuropathic pain induced by partial ligation of the sciatic nerve. Specifically, i.c.v. (Huang et al., 2007) or s.c. injection (Smith et al., 2007) of thioperamide directly into the operated hindpaw resulted in a significantly reduced mechanical withdrawal threshold as compared to controls. On the other hand, systemic (i.p.) injection of thioperamide significantly increased mechanical withdrawal threshold indicating an analgesic effect (Huang et al., 2007). The reason for this discrepancy may lie in the drug's dual affinity for both H_3 and H_4 receptors (e.g., the effect of thioperamide on neurotransmitter release in the anterior hypothalamic area of rats is nonreversible by an H_3 receptor agonist, suggesting the involvement of H_4 receptors; Yamamoto, Mochizuki, Okakura-Mochizuki, Uno, & Yamatodani, 1997) and on the behavioural effects resulting from the route (localized vs. systemic) and dose of thioperamide administration. In addition, the involvement of other histaminergic mechanisms of action in the behavioural effects

produced by thioperamide is suggested by the observation that thioperamide increases the density of intact mast cells in the injured nerve (Smith et al., 2007). While nerve injury causes a decrease in mast cell numbers as a consequence of degranulation (Zuo et al., 2003), thioperamide's action leads to an opposite effect that may represent a prevention of mast cell degranulation and stabilization or redistribution of mast cells in the injured nerve that theoretically would result in the inhibition of hyperalgesia, rather than its enhancement. This effect could be linked to the observation that histamine (acting through H₁ and H₃ receptors) inhibits the release of the pro-inflammatory cytokine **TNF- α** from alveolar macrophages (Sirois, Ménard, Moses, & Bissonnette, 2000), and antagonism of H₃ receptors on macrophages resulted in an increase in TNF- α and, subsequent, enhancement of mechanical hyperalgesia (Smith et al., 2007).

Taken together, the interpretation of the thioperamide data is complicated further since the drug has high affinity, not only for H₃ and H₄ receptors but also for **5-HT₃ receptors** (Leurs et al., 1995). Studies with more selective H₃ receptor antagonists/inverse agonists suggest that these ligands may be beneficial for the improvement of mechanical and cold hypersensitivity associated with neuropathic pain, particularly given their ability to modulate histamine levels, as well as several neurotransmitters, including ACh, histamine, noradrenaline, dopamine, and SP. However, due to the wide presynaptic and postsynaptic distribution of H₃ receptors throughout the CNS and PNS, more research is certainly needed to clarify the involvement of peripheral, spinal, and brain H₃ receptors in various neuropathic pain states, thus determining their full potential in neuropathic pain.

3.3 | H₄ receptor ligands and neuropathic pain

The H₄ receptor, which has low homology with other histamine receptors, can be primarily found in bone marrow, intestinal tissue, spleen, thymus, and also in various immune cells, such as T cells, mast cells, neutrophils, and eosinophils, showing modulatory effects on these cells, including activation, migration, and production of cytokines and chemokines, suggesting its principal role in the regulation of immune/inflammatory mechanisms (Takeshita, Sakai, Bacon, & Gantner, 2003; Zhu et al., 2001). Interestingly, recent reports also indicate the presence of H₄ receptors on peripheral sensory nerves, in the DRG, with more intense staining of small- and medium-diameter cells, and in the spinal cord, especially laminae I and II (Sanna, Lucarini, et al., 2017; Strakhova et al., 2009). This neuronal localization supports H₄ receptors involvement in the regulation of neuronal function related to the modulation of nociceptive transmission (Sanna, Ghelardini, Thurmond, Masini, & Galeotti, 2017; Sanna, Lucarini, et al., 2017).

The involvement of H₄ receptors in both acute (Galeotti, Sanna, & Ghelardini, 2013) and persistent inflammatory pain (Hsieh et al., 2010) is relatively well documented, and recently, the role of H₄ receptors in the modulation of neuropathic pain was identified in H₄ receptor-KO mice through the observation that these animals, when subjected to neuropathic pain, induced by spared nerve injury of sciatic nerve, showed enhanced hypersensitivity to mechanical and thermal stimuli compared to wild-type controls (Sanna, Ghelardini, et al., 2017).

Interestingly, H₄ receptor deficiency does not support a role for H₄ receptors in the physiological maintenance of pain threshold, as H₄ receptor-KO mice did not show any change in thermal or mechanical nociceptive thresholds, suggesting that the H₄ receptor is specifically involved in the regulation of hypersensitivity associated with pathological chronic pain induced by nerve injury (Sanna, Ghelardini, et al., 2017). This observation in H₄ receptor-KO neuropathic mice is particularly important as H₄ receptor mRNA expression in humans and rodents supports their involvement in the regulation of neuronal function, including regulation of neuropathic pain. The controversy around the generation of consistently specific H₄ receptor antibodies highlights the need for cautious interpretation of some of the immunohistochemical outcomes (Beermann, Seifert, & Neumann, 2012; Gutzmer et al., 2012; Schneider & Seifert, 2016). In line with the observation from H₄ receptor KO mice, blockade of H₄ receptors by the specific H₄ receptor antagonist JNJ7777120, injected s.c. directly into the operated hindpaw, resulted in a significant increase in mechanical hyperalgesia compared to controls (Smith et al., 2007). Subsequently, activation of H₄ receptors by localized administration of potent and selective agonists, **ST-1006** (i.c.v.) and **VUF8430** (i.c.v., intrathecally, and s.c. directly into the operated hindpaw), resulted in a significantly reduced mechanical and thermal withdrawal threshold in mice subjected to neuropathic pain induced by spared nerve injury or partial nerve ligation of the sciatic nerve (Sanna et al., 2015; Sanna, Lucarini, et al., 2017; Smith et al., 2007). The analgesia produced by VUF8430 has been shown to be associated with a reduction in neuroinflammation and oxidative stress mediated by neuronal H₄ receptors in the spinal cord and sciatic nerve (Sanna, Lucarini, et al., 2017), and the involvement of H₄ receptors in the behavioural effects produced by ST-1006 and VUF8430 was confirmed with **JNJ10191584**, H₄ receptor antagonist also known as VUF6002, which fully prevented the analgesic effects produced by these H₄ receptor agonists (Sanna et al., 2015).

Interestingly, similar to the H₃ receptor, pharmacological studies using agonists and antagonists of H₄ receptors demonstrate that these drugs can have different effects on the nociceptive threshold depending on the routes of administration and target cells (Popiolek-Barczyk et al., 2018; Sanna et al., 2015). In contrast to the studies above that used H₃ receptor agonists/antagonists after localized application, the antagonism of H₄ receptors produced by systemic administration resulted in the alleviation of mechanical and cold hypersensitivity associated with neuropathic pain (chronic constriction injury model). Studies using TR-7, a selective H₄ receptor antagonist, elicited a strong analgesic effect after a single systemic (i.p.) dose, which was as effective as **morphine**, a gold standard in pain treatment (Popiolek-Barczyk et al., 2018). In addition, JNJ7777120 reduced mechanical hypersensitivity after a systemic (i.p.) administration in neuropathic pain (chronic constriction injury model and spinal nerve ligation model; Hsieh et al., 2010). Given that H₄ receptors are expressed on the immune cells, in addition to the well-documented involvement of H₄ receptors in the regulation of immune/inflammatory mechanisms (Takeshita et al., 2003; Zhu et al., 2001), it is possible that the antinociceptive action of H₄ receptor antagonists, particularly after systemic administration,

may result from a reduction in ongoing inflammatory processes at the site of nerve injury, since the analgesic effect produced by JNJ7777120 was weaker (secondary) than its anti-inflammatory effect (Hsieh et al., 2010). An underlying mechanism may be associated with stabilization of mast cells that are known to regulate the recruitment of neutrophils and macrophages and, subsequently, to modulate the development of hyperalgesia in neuropathic pain (Smith et al., 2007; Zuo et al., 2003). It should be further noted that similar observations have been described for the closely related H₃ receptor.

The H₄ receptor is known to activate the MAPK signalling pathway in mast cells (Desai & Thurmond, 2011). Interestingly, Sanna et al. (2015, 2018) also identified the effect of H₄ receptor stimulation on the activity of the MAPK signalling pathway in neurons. They demonstrated that modulation of this signalling pathway within the neurons of the DRG, spinal cord, and sciatic nerve underpinned H₄ receptor agonist-induced antiallodynic activity. They also revealed that neuropathic pain hypersensitivity observed in H₄ receptor-KO mice is associated with an overactivation of the spinal ERK-cAMP response element-binding protein pathway in DβH immunoreactive neurons, supporting a potential association between the noradrenergic system and H₄ receptor-mediated analgesia. In summary, increasing evidence arising from H₄ receptor KO mice and the use of selective ligands support H₄ receptor as an interesting neuronal target for the treatment of chronic, particularly neuropathic, pain.

4 | HISTAMINE AND NON-NEURONAL CELLS IN NEUROPATHIC PAIN

Following peripheral nerve injury, the immune system seems to play a vital role in the development of persistent inflammation and chronic neuropathic pain (Marchand, Perretti, & McMahon, 2005). Non-neuronal astrocytes, satellite glia cells, microglia, and mast cells play key roles in communication between the immune system and the CNS via the production of neuroinflammatory mediators, including histamine, 5-HT, chemokines, and growth factors (Zhuang, Gerner, Woolf, & Ji, 2005). The neuroimmune interactions between these two systems may reflect distinct roles in the development of chronic neuropathic pain (Zhao et al., 2017). Stimulation of H₁ receptors via a PKC/MAPK/MEK1 signalling pathway has recently been shown to elicit release of the key pro-inflammatory cytokines IL-1β and IL-6 with, subsequent, regulation of nerve growth factor release from astrocytes (reviewed recently in Jurič, Kržan, & Lipnik-Stangelj, 2016). Satellite glial cells, prominent in the PNS, including the DRGs, with active roles in persistent neuropathic pain are also known to secrete the cytokine IL-6 in the chronic constriction injury neuropathic pain model, but the identity profile of the histamine receptor in these cells has yet to be established (Dubový, Klusáková, Svíženská, & Brázda, 2010). Activated microglia also release a myriad of pro-inflammatory cytokines, including notably, IL-6, IL-1β, and TNF-α (Kempuraj et al., 2016; Mika, Zychowska, Popiolek-Barczyk, Rojewska, & Przewlocka, 2013). H₃ and H₄ receptor activation of primary and clonal microglia has been shown to inhibit these cytokines (Ferreira et al., 2012).

Mast cells are professional cellular suppliers of histamine and contribute to the histamine-based effects in neuropathic pain. For example, mast cell depletion prevented mechanical allodynia in a mouse model of postoperative pain (Kaur, Singh, & Jaggi, 2017). Recently, it was shown that the administration of azelastine hydrochloride, a second-generation H₁ receptor antagonist and mast cell stabilizer, blocked the development of mechanical allodynia and inhibited mast cell degranulation in mice with oxaliplatin-induced mechanical allodynia pain. The H₁ and H₄ receptors are likely molecular players in this process (Sakamoto, Andoh, & Kuraishi, 2016). For example, genetically silencing the H₄ receptor inhibited the production of IL-1β for human mast cells (Ebenezer, Prasad, Rajan, Thangam, & Transduction, 2018), and H₄ receptor activation was shown to stimulate a number of cytokines, including IL-6 (Jemima, Prema, & Thangam, 2014). In addition, while H₁ and H₂ receptor antagonism reduced hypersensitivity following nerve injury, it is possible that histamine released by mast cells contributes to the recruitment of neutrophils and macrophages in neuropathic pain and, acting via these histamine receptors, contributes to the regulation of hypersensitivity in this type of chronic pain (Jaggi et al., 2017; Smith et al., 2007; Zuo et al., 2003). There is an important aspect associated with H₂ receptor antagonism, which should be considered for its therapeutic potential in neuropathic pain control. In vitro studies using CHO and HEK-293 cells identified time- and dose-dependent up-regulation of H₂ receptors upon long-term exposure to H₂ receptor antagonists (e.g., ranitidine), which may underlie the development of tolerance after prolonged clinical use of these ligands and result in the rebound hypersecretion of gastric acid and anaphylaxis that can occur after withdrawal of treatment (Allen, Chazot, & Dixon, 2018; Smit et al., 1996). Thus, side effects linked to pharmacological tolerance may potentially compromise long-term efficacy and tolerability of H₂ receptor antagonists in neuropathic pain. Little is known about the role of the H₃ receptors in non-neuronal cells in neuropathic pain states.

Overall, non-neuronal cells play a key, but poorly, defined role in the mechanisms underlying histamine-mediated neuropathic pain. We propose that neuronal H₁ and H₄ receptors (Ferreira et al., 2012) may orchestrate these mechanisms, with IL-6 and IL-1β cytokines as common denominator mediators. Further complications arise from the recent observation that activated mast cells trigger microglial activation (Zhang, Wang, Dong, Xu, & Zhang, 2016). These cell types and their interactions may potentially go some way to explain the paradoxical effects of histamine ligands, particularly for the H₄ receptor, seen in animal pain models.

5 | HISTAMINE AND ITS INTERACTION WITH OPIOID SYSTEM IN NEUROPATHIC PAIN

Interestingly, in neuropathic pain, high doses of opioids are required to achieve pain relief, and pharmacological tolerance to analgesic effect of opioids develops rapidly (Osikowicz, Mika, Makuch, & Przewlocka, 2008). This phenomenon significantly restricts the clinical usefulness of opioids. In addition, the misuse of and addiction to

opioids, including prescription pain relievers, morphine and heroin, as well as synthetic opioids, such as fentanyl, is a serious international crisis that affects public health as well as social and economic welfare (Lipman & Webster, 2015).

An interaction between histaminergic and opioidergic systems within the CNS was suggested nearly 30 years ago, through an observation that morphine administration resulted in the release of histamine and its increased turnover in the periaqueductal grey (Nishibori, Oishi, Itoh, & Saeki, 1985), suggesting that analgesia produced by opioids may be associated with the stimulation of histamine receptors at the supraspinal level. There are also data suggesting that ligands of histamine receptors may modulate the analgesic action of opioids; however, the site and mode of this interaction differ between the spinal or supraspinal level, and depend on the subtype of histamine receptor involved (Mobarakeh et al., 2002; Mobarakeh et al., 2006; Mobarakeh, Takahashi, & Yanai, 2009). Specifically, a series of studies over the last two decades has shown that in H_1 , H_2 , or H_3 receptor-KO mice, morphine-induced antinociception was significantly augmented when compared to the wild-type controls in models of acute pain. H_1 receptor-KO mice showed a reduced spontaneous nociceptive threshold as they responded to significantly lower pain stimuli when compared to their controls (Mobarakeh et al., 2002), while thresholds for pain perception in H_2 receptor-KO mice were higher when compared to their corresponding controls (Mobarakeh et al., 2006). Intrathecal administration of morphine in H_1 and H_3 receptor-KO mice and i.c.v. morphine injection in H_2 receptor-KO mice produce enhanced analgesic effects (Mobarakeh et al., 2002; Mobarakeh et al., 2006). Interestingly, pharmacological blockade of H_1 and H_3 receptors by either intrathecal administration of the first-generation antihistamine chlorpheniramine (H_1 receptor antagonist) or thioperamide (H_3 receptor antagonist, H_3/H_4 receptor inverse agonist), or H_2 receptor antagonism, produced by zolantidine (i.c.v. route), resulted in the potentiation of the morphine analgesic effect (Mobarakeh et al., 2002; Mobarakeh et al., 2006). These behavioural studies, in both KO mice and involving pharmacological interventions, clearly demonstrated that blocking H_1 , H_2 and H_3 receptors in combination with morphine may have beneficial effects on analgesia and suggested that endogenous histamine may exert an inhibitory effect on morphine-induced analgesia acting via H_1 and H_3 receptors at the spinal cord level and via H_2 receptors at the supraspinal level.

Importantly, the observations observed with H_3 receptor-KO mice are consistent with a pharmacological study using a preclinical model of neuropathic pain induced by chronic constriction injury of the sciatic nerve. Here, Popiolek-Barczyk et al. (2018) showed that blockade of H_3 receptors by a selective antagonist (E-162) significantly enhanced morphine antinociception assessed with both mechanical and cold stimuli. Pharmacological analysis of these effects revealed an additive effect. Interestingly, Popiolek-Barczyk et al. (2018) also showed that TR-7, a selective H_4 receptor antagonist, significantly enhanced morphine antinociception in neuropathic pain. This latter study is the first demonstration of the involvement of H_4 receptors in the regulation of morphine efficacy in chronic pain.

To the best of our knowledge, the literature does not provide evidence for the mechanisms underlying histamine and opioid system interactions, in relation to the modulation of morphine analgesic effects. Given that the analgesic effects produced by modulation of the activity of both the histamine and opioid systems could be associated with blocking SP release from peripheral nerve terminals (Barnes et al., 1986; Przewłocki & Przewłocka, 2001), it is possible that an interaction that would result in potentiation of analgesic efficacy of morphine may involve, together with other possible mechanisms, the inhibition of peripheral SP accumulation. Such an outcome may be useful for the management of neuropathic pain, particularly when peripheral administration of drugs is possible, thus affording reduction of the undesired secondary effects associated with opioid administration and peripheral mechanisms of action (e.g., constipation). However, centrally acting drugs administered by peripheral routes should be taken into consideration due to the potential serious interactions related to their pharmacodynamics and central mechanisms of action. For example, chlorpheniramine (a first-generation H_1 receptor antagonist) was reported to potentiate fentanyl-induced sedation and respiratory depression after surgery (Anwari & Iqbal, 2003).

6 | CONCLUSIONS AND FUTURE DIRECTIONS

Findings from the last two decades indicate that selective pharmacological antagonism of neurons expressing H_3 receptors could provide important and promising therapeutic approaches for the control of mechanical and cold hypersensitivity in peripheral neuropathies (Table 1). The analgesic effectiveness of H_3 receptor antagonists/inverse agonists was comparable to gabapentin and pregabalin, first-line treatments for neuropathic pain. Importantly, multiple examples of behavioural, electrophysiological, and molecular evidence strongly support the rationale for this neuropathic pain strategy, particularly given their ability to modulate histamine levels as well as several neurotransmitters critical for chronic pain processing. Moreover, the recent registered approval of pitolisant (Wakix™), an antagonist/inverse agonist of H_3 receptors, for the treatment of narcolepsy in patients, has opened the door for the potential use of H_3 receptor ligands for other conditions, including chronic neuropathic pain. However, due to the wide presynaptic and postsynaptic distribution of H_3 receptors throughout the CNS and PNS, more research is certainly needed to clarify the involvement of peripheral, spinal, and brain H_3 receptors in various pain states, before determining their full potential in neuropathic pain.

Recent findings also suggest the use of centrally permeable H_2 receptor antagonists as promising new drug candidates for the treatment of neuropathic pain, in view of their analgesic effects and metabolic stability. Interestingly, however, despite the discovery of the most recently discovered histamine receptor, the role of the H_4 receptor in neuropathic pain transmission is still controversial after nearly 20 years, with apparent confounding effects of both agonists and antagonists on hypersensitivity associated with neuropathic pain. This

may be due to biased signalling of histamine and H₄ receptor agonist ligands and differential effects on multiple signalling pathways in central and peripheral parts of the sensory nervous system. Furthermore, the paucity of detailed mechanistic definitions of histamine-mediated analgesia, and the additive effects with the opioid system, requires attention to provide a rationale to the field of histamine and development of neuropathic pain control therapeutics.

A better understanding of the interaction between histaminergic signalling pathway molecules (Figures 1–3) and histamine receptors may result in the identification of further novel pharmacological targets to improve neuropathic pain control. The literature available provides some evidence for potential pharmacological target molecules. One potential strategy exploits the role of Ca²⁺ channels in the regulation of cellular excitability associated with nociception (e.g., N-type Ca²⁺ channels). Evidence has shown that Ca²⁺ channel blockers (e.g., **ω-conotoxin-MVIIA/Prialt**) offer interesting analgesic potential in treating neuropathic pain (Vanegas & Schaible, 2000). However, there is no evidence for the effect produced by a combination of Ca²⁺ channel blockers and histamine receptor ligands, and we propose that their interaction should be taken into consideration. Another potential target involves the contribution of the MAPK/ERK signalling pathway to the regulation of pain hypersensitivity. Recently, Sanna et al. (2015) showed that H₄ receptor stimulation, which led to analgesic activity in neuropathic pain, was modulated by MAPK/ERK signalling in the neurons of the DRG, spinal cord, and sciatic nerve. While the MAPK/ERK signalling pathway regulates pain sensitivity and, for a while, has been considered as a target for the treatment of neuropathic pain (Ma & Quirion, 2005), further studies on the interaction between this pathway and H₄ receptors may lead to the identification of more efficient therapeutic strategies to control neuropathic pain.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org/>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Christopoulos et al., 2017; Alexander, Fabbro et al., 2017; Alexander, Peters et al., 2017; Alexander, Striessnig et al., 2017).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Ilona Obara  <https://orcid.org/0000-0002-8906-2771>

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