BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.02093.x
www.brjpharmacol.org

REVIEW

Histamine H_3 receptor antagonists in relation to epilepsy and neurodegeneration: a systemic consideration of recent progress and perspectives

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Keywords
histamine H_3 receptor antagonists; epilepsy; neurodegeneration and neurotoxicity; H_3 receptor signalling pathways

Received
9 March 2012
Revised
3 May 2012
Accepted
12 June 2012

The central histaminergic actions are mediated by H_1, H_2, H_3 and H_4 receptors. The histamine H_3 receptor regulates the release of histamine and a number of other neurotransmitters and thereby plays a role in cognitive and homeostatic processes. Elevated histamine levels suppress seizure activities and appear to confer neuroprotection. The H_3 receptors have a number of enigmatic features like constitutive activity, interspecies variation, distinct ligand binding affinities and differential distribution of prototypic splice variants in the CNS. Furthermore, this Gi/Go-protein-coupled receptor modulates several intracellular signalling pathways whose involvement in epilepsy and neurotoxicity are yet to be ascertained and hence represent an attractive target in the search for new anti-epileptogenic drugs. So far, H_3 receptor antagonists/inverse agonists have garnered a great deal of interest in view of their promising therapeutic properties in various CNS disorders including epilepsy and related neurotoxicity. However, a number of experiments have yielded opposing effects. This article reviews recent works that have provided evidence for diverse mechanisms of antiepileptic and neuroprotective effects that were observed in various experimental models both *in vitro* and *in vivo*. The likely reasons for the apparent disparities arising from the literature are also discussed with the aim of establishing a more reliable basis for the future use of H_3 receptor antagonists, thus improving their utility in epilepsy and associated neurotoxicity.

Abbreviations

[^{35}S]-GTPγS, [^{35}S]-guanosine 5′-γ-thiotriphosphate; $[Ca^{2+}]_i$, intracellular calcium; 3-NP, 3-nitropropionic acid; AA, arachidonic acid; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; AEDs, antiepileptic drugs; CaMKII, Ca^{2+}-activated calmodulin kinases; CREB, cAMP-responsive-element-binding protein; HDC, histidine decarboxylase; *h*H_3 receptor, human H_3 receptor; HSPs, heat shock proteins; ICER, inducible cAMP early repressor; IPI, initial precipitating injury; KA, kainic acid; MAPKAPK2, MAPK-activated protein kinase 2; MEK, MAP/ERK kinase; NHE, Na^+/H^+ exchanger; GluN2B, NMDA receptor subunit 2B; PD, Parkinson's disease; SE, status epilepticus; TLE, temporal lobe epilepsy; TMN, tuberomammillary nucleus

Histamine has been one of the most studied substances in medicine for a century, regulating a wide spectrum of activities, including its function in neurotransmission (Brown *et al*., 2001). The association between the histaminergic system with the pathogenesis of epilepsy, which is currently the subject of extensive evaluation, is still in its infancy, owing to the complex brain neurophysiology of histamine (Haas *et al*., 2008) and pleiotropic receptor ligand pharmacology (Leurs *et al*., 2005; Esbenshade *et al*., 2008; Tiligada *et al*., 2009). Our understanding of the pathophysiology of epilepsy is mostly confined to the conventional theory of deranged inhibitory GABAergic and protracted excitatory glutamatergic neurotransmission in excitotoxic neuronal death (reviewed by Naylor, 2010; Werner and Coveñas, 2011; Rowley *et al*., 2012). The imbalance could be modulated by various other neurotransmitter systems including the histaminergic system. The latter, through H_3 heteroreceptors, modulates the release of a wide spectrum of vital neurotransmitters, for example, GABA, glutamate, dopamine, 5-HT, noradrenaline and acetylcholine, in a pathway-dependent manner (reviewed by Passani *et al*., 2007; Haas *et al*., 2008). Again, histamine release is not only regulated by its own H_3 autoreceptor system but also by GABA via $GABA_A$ and $GABA_B$ receptors and by glutamate via NMDA receptors (Okakura *et al*., 1992; Okakura-Mochizuki *et al*., 1996; Sherin *et al*., 1998).

Excitotoxicity is considered to be the key mechanism underlying neurodegenerative processes including epileptic seizures (Choi, 1992). Neurodegeneration followed by neuronal cell death resulting from excessive activation of excitatory ionotropic glutamate receptors [NMDA, AMPA and kainic acid (KA)] or malfunctioning of the inhibitory mechanism due to altered functioning of $GABA_A$ receptor, usually underlies the dissemination of epileptic activity (reviewed by Acharya *et al*., 2008). The compensatory yet abnormal neuronal activities that follow, viz. mossy fibre sprouting, significantly modify the neuronal organization and alter the propagation of neurotransmission processes that is attributable to the epileptogenic mechanisms (Dichter, 2009). Epileptogenesis refers to the progressive transformation of normal brain to a hyperexcitable epileptic brain, after an initial precipitating injury (IPI), for example status epilepticus (SE), and continues even after the withdrawal of the inciting stimulus. This is a characteristic of temporal lobe epilepsy (TLE), the most intractable form of epilepsy (Acharya, 2002; Loscher and Brandt, 2010). The conventional and new antiepileptic drugs (AEDs) affect seizure expression, merely providing symptomatic treatment without having any influence on the course of the disease (epileptogenesis). The current consensus is to employ anti-epileptogenic strategies for treating TLE (Walker, 2007; Acharya *et al*., 2008; Pitkanen, 2010). Hence, there is a growing interest that the AEDs, besides controlling seizure activity, must also prevent concurrent injury responses that result in epileptogenesis in the hippocampal structures, a phenomenon linked to the transformation of a normal non-epileptic brain to a hyperexcitable epileptic brain in which recurrent, spontaneous seizures occur. In fact, epilepsy treatment has always been associated with the protection of neural tissue, since it intends to diminish the duration or totally suppress seizures. Even though the debate on the capacity of simple seizures to induce neuronal injury is still in progress, there is compelling evidence for the disastrous effects of prolonged episodes of status epilepticus (Willmore, 2005; Acharya *et al*., 2008). The role of the brain histaminergic system in neuroprotection remains a challenging area of research that is currently under consideration. Based on recent findings, which include changes in H_1 and H_3 receptor expression in a KA-induced epileptic model, it has been proposed that the brain histaminergic system is involved in experimental SE and subsequent neurodegeneration (Jin *et al*., 2005; Lintunen *et al*., 2005).

Histamine is considered to be an anticonvulsive neurotransmitter as its low levels are associated with convulsions and seizures (Kiviranta *et al*., 1995; Chen *et al*., 2003; Hirai *et al*., 2004). Until now, research on the anticonvulsive role of histamine has largely focused on electrically- or PTZ-induced seizures (Vohora *et al*., 2000; 2001; Yawata *et al*., 2004). However, an understanding of the possible role of histamine in temporal lobe epilepsy and the brain regions affected has begun to evolve (Jin *et al*., 2007; Kukko-Lukjanov *et al*., 2012). Prolonged release of histamine in response to brain ischaemic insults and alleviation of neuronal damage upon post-ischaemic histamine administration suggests it has a neuroprotective role (reviewed by Adachi, 2005). Histaminergic drugs, most importantly H_3 receptor antagonists or inverse agonists, which are considered to be a class of perspective drugs for the treatment of diverse neurological and neuropsychiatric disorders (reviewed by Leurs *et al*., 2011; Passani and Blandina, 2011), in view of the findings from various basic experimental models of epilepsy in rodents, are envisaged to possess promising anticonvulsive properties (Vohora *et al*., 2000; 2001; 2010; Harada *et al*., 2004a,b).

In this review, an attempt has been made to scrutinize the recent experimental evidence that has evoked the possibility that the histaminergic system, via modulation of H_3 receptor function, can be engaged to mediate a neuroprotective effect in epilepsy-related neurotoxicity and also to address the possible mechanisms involved, which would explain the above effects. Histamine and various agents, which act by modulating the histaminergic system, especially H_3 receptor antagonists, and their impact on epileptogenesis are then examined with particular reference to the neuroprotective action of some of these molecules. The core of the review deals with the current status of the literature on the use of some of these inhibitors as antiepileptic and neuroprotective agents as well as on their possible role in intervening in disease modifications of the brain (epileptogenesis). Probable explanations for many of the conflicting results arising from the literature are discussed in view of establishing a more reliable platform for future use of histaminergic agents to treat epilepsy and associated neurotoxicity.

Histaminergic system in CNS

In the CNS, the synthesis of histamine [2-(4-imidazolyl)-ethylamine] from 1-histidine by the catalytic activity of the rate-limiting enzyme histidine decarboxylase (HDC, EC 4.1.1.22; Moya-Garcia *et al*., 2005) takes place in a restricted population of neurons located in the tuberomammillary nucleus (TMN) of the posterior hypothalamus (Panula *et al*.,

1984; Watanabe *et al*., 1984; Wouterlood *et al*., 1986). They give rise to widespread and diffuse projections extending through the basal forebrain virtually to the entire brain including the cortex, striatum, thalamus, hippocampus, hypothalamus, locus coeruleus and spinal cord (Watanabe *et al*., 1984; Panula *et al*., 1990; Zimatkin *et al*., 2006). This morphology renders histamine to be able to act as a neurotransmitter and neuromodulator of a wide spectrum of physiological functions and behaviours of the CNS, such as the circadian rhythms, catalepsy, energy homeostasis, thermoregulation, neuroendocrine and cardiovascular control, drinking and feeding, learning and memory, locomotion, sexual behaviour, analgesia and emotion (reviewed by Brown *et al*., 2001; Passani *et al*., 2007; Yanai and Tashiro, 2007; Haas *et al*., 2008).

Histamine H_3 receptor

The histamine neuroreceptor system is one of the major aminergic systems exerting key neurological functions via pharmacologically distinct subtypes of histamine receptors, which belong to a large superfamily of GPCRs that are characterized by the presence of seven putative transmembrane spanning domains (Leurs *et al*., 2005; Parsons and Ganellin, 2006). To date, histamine has been recognized to be an endogenous ligand for four subtypes of metabotropic histamine receptor (H_{1-4}; Parsons and Ganellin, 2006; Nuutinen and Panula, 2010), of which H_{1-3} receptors are very widely expressed throughout the mammalian brain (Garbarg and Schwartz, 1985; Hill *et al*., 1997; Tashiro and Yanai, 2007). For the H_3 receptor, so far, six isoforms have been reported with varying distribution (H_{3A-F}; Lovenberg *et al*., 1999; Drutel *et al*., 2001; Bakker *et al*., 2006) and pharmacological properties (reviewed in Hancock *et al*., 2003). Both the H_{3A} and H_{3D} isoforms contain the full-length third intracellular loop but have different C-termini. All the other isoforms have deletions in that loop (H_{3B} and H_{3E}: 32 amino acids; H_{3C} and H_{3F}: 48 amino acids). Isoforms H_{3A-C} have the same C-terminus, while isoforms H_{3E-F} have an alternative C-terminus (reviewed in Leurs *et al*., 2005; Arrang *et al*., 2007).

Numerous studies have established that all subtypes (H_1 and H_2) are located postsynaptically and are found in the CNS and periphery (reviewed in Parsons and Ganellin, 2006), whereas the recently discovered H_4 receptor is found predominantly in mast cells and leucocytes (reviewed by Oda and Matsumoto, 2001; Leurs *et al*., 2009), although their presence in the CNS has also been detected (Connelly *et al*., 2009); with the exception of the H_3 receptor, which was originally characterized as a presynaptic autoreceptor that is located on histaminergic and other cell somata, dendrites and axonal varicosities (Arrang *et al*., 1983; Lovenberg *et al*., 1999). Although, later on, a detailed mapping of the H_3 receptors in rat brain revealed their presence post-synaptically on the perikarya, dendrites and projections of many neuronal populations (Pillot *et al*., 2002), but their postsynaptic physiological role is yet to be elucidated (reviewed in Arrang *et al*., 2007). Both rat and human H_3 receptors (*h*H_3 receptors) again have the striking feature of being constitutively (or spontaneously) active, by virtue of their existence in their active conformation even in the absence of histamine (agonist), thereby negatively regulating the synthesis and release of histamine (Schwartz *et al*., 1990). Inverse agonists by attenuating this constitutive inhibitory effect enhance histamine release (Jansen *et al*., 1998; Morisset *et al*., 2000; Rouleau *et al*., 2002; Arrang *et al*., 2007).

The relative expression of histamine H_3 receptors is very high in the CNS, where they participate in the modulation of arousal, learning and memory and food intake by means of their autoreceptor and heteroreceptor functions. So far, the H_3 receptor has been postulated to be a good target for drug discovery for a variety of CNS conditions (Gemkow *et al*., 2009; Schwartz, 2011). The H_3 receptor, being an auto- as well as hetero-receptor, was subsequently found to restrict the release of histamine and other neurotransmitters, including acetylcholine, dopamine, glutamate, noradrenaline and 5-HT (Schwartz *et al*., 1990; Schlicker *et al*., 1994). Consequently, specific ligands for the H_3 receptor show potential therapeutic effects in models of obesity, depression, mood disorders, neuropathic pain, epilepsy, sleep–wake disorders including narcolepsy and cognitive and sensorimotor deficits that are considered to be the more common deleterious features of CNS disorders such as Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD) and schizophrenia (Fox *et al*., 2005; Leurs *et al*., 2005; Nuutinen and Panula, 2010; Passani and Blandina, 2011; Schwartz, 2011).

H_3 receptor signalling pathways

The seminal work of Arrang *et al*. (1983) was the first to identify the third histamine receptor and this has opened a new chapter in the pharmacology of histamine. With the cloning of the *h*H_3 receptor gene pioneered by Tim Lovenberg in 1999, H_3 receptor research has received a tremendous boost and enormous progress has been made in the field ever since. At present, we are buoyed by the detailed knowledge of its modulation of several signalling pathways based on the findings in the last 10 years. The notion of G-protein (especially G_i/G_o) involvement in the H_3 receptor was confirmed by the heterologous expression of the H_3 receptor (Lovenberg *et al*., 1999) and this was further substantiated by the reported inhibitory effects of G-protein toxins, such as cholera and *Pertussis* toxin, on H_3 receptor function (Rouleau *et al*., 2002) and [^{35}S]-GTPγS binding studies in rat brain (Clark and Hill, 1996).

Studies using recombinant cell systems have revealed that brain H_3 receptors are coupled to $G_{i/o}$-proteins modulating protein kinases such as cAMP-dependent protein kinase (PKA), ERK2 (Giovannini *et al*., 2003) and GSK-3β (Bongers *et al*., 2007b). Thus, a number of signal transduction pathways have been identified as being modulated by H_3 receptors (Figure 1), including inhibition of AC and activation of MAPK (reviewed by Leurs *et al*., 2005; Bongers *et al*., 2007a). H_3 receptor activation of $G_{i/o}$-proteins might also lead to the activation of PLA_2 to induce the release of arachidonic acid (AA; Rouleau *et al*., 2002), inhibition of the Na^+/H^+ exchanger (NHE; Silver *et al*., 2001) as well as modulation of intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels (Silver *et al*., 2002). In view of the interest in the H_3 receptor as a potential therapeutic target, each of these signalling path-

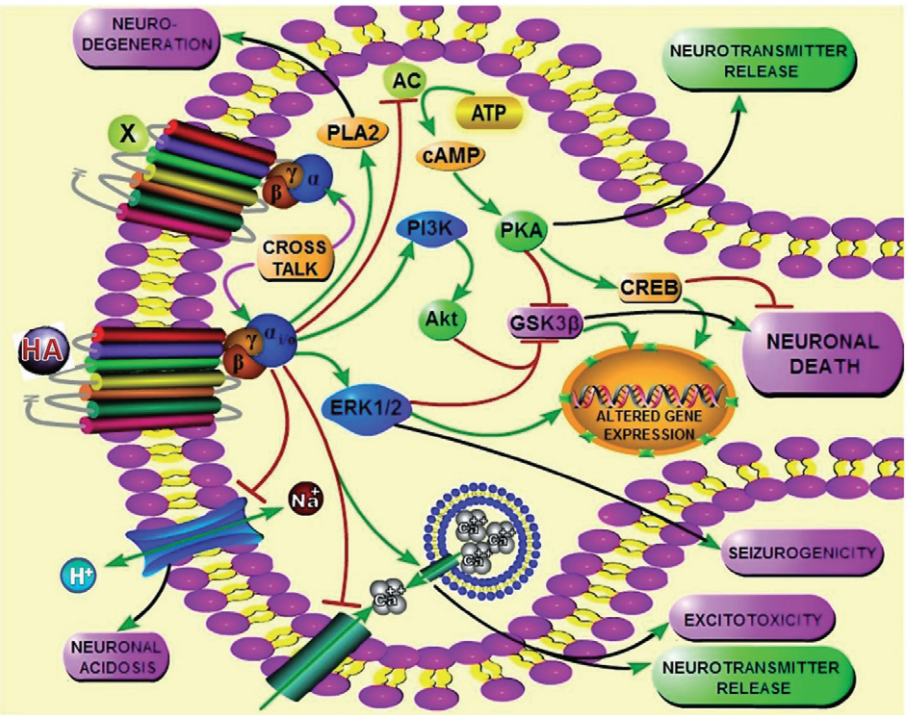

Figure 1

The schematic diagram is a hypothetical depiction of the H_3 receptor-mediated signalling pathways in the CNS and their probable implications. Activation of H_3 receptor, constitutively or in presence of an agonist, leads to the activation of many $G_{i/o}$-associated intracellular pathways. Active $G_{i/o}$-proteins negatively couple AC, thereby inhibiting the cAMP/PKA cascade and subsequent lowering of cAMP responsive element binding protein (CREB), a pro-survival transcription factor. Reduction in PKA activity may decrease release of neurotransmitters, for example histamine (HA), GABA, etc. Additionally, H_3 receptor activation also activates PI3K and MAPK pathways. Activated PI3K then activates Akt, a serine threonine kinase, which phosphorylates and hence inactivates pro-apoptotic GSK-3β. In the MAPK pathway, especially p44 and p42 MAPK (ERK1/2) are coupled to H_3 receptors; activated ERK has also been linked to epilepsy. The other three pathways known so far that are modulated upon H_3 receptor activation include increased activity of the enzyme PLA_2, whose inhibition confers neuroprotection in epileptic models; mobilization of intracellular Ca^{2+} $[Ca^{2+}]_i$; and finally the inhibition of Na^+/H^+ exchanger (NHE), a protein that buffers intra-neuronal pH and it's defective functioning is also implicated in epilepsy. Also, H_3 receptors possibly influence the function of other GPCRs and *vice versa* (e.g. dopamine D_1 receptor) by virtue of cross talk in heteromer containing cells.

ways is discussed below and any evidence germane to epilepsy (if any) and neurodegeneration is cited.

PKA/cAMP/CREB pathway

AC catalyses the formation of cAMP, which in turn, activates PKA and, subsequently, induces cAMP-responsive-element-binding protein (CREB) to modulate gene transcription. The H_3 receptor negatively couples to AC; hence, H_3 receptor activation lowers cAMP levels and reduces downstream events, such as CREB-dependent gene transcription (Lovenberg *et al.*, 1999). The lowering of intracellular levels of cAMP through the activation of H_3 autoreceptors (by an agonist or via a constitutive property) results in the modulation of histamine synthesis in histaminergic nerve terminals through the AC/PKA pathway (Gomez-Ramirez *et al.*, 2002). Many classical H_3 receptor antagonists, for example thioperamide, clobenpropit, ciproxifan, were found to reverse this process in various transfected cell lines (Morisset *et al.*, 2000; Wieland *et al.*, 2001). Similarly, ABT-239 (H_3 receptor antagonist) restored cortical CREB level and increased its phosphorylation in mice (Bitner *et al.*, 2011).

The transcriptional activation of CREB is induced by an array of kinases including PKA (Gonzalez and Montminy, 1989), Ca^{2+}-activated calmodulin kinases (CaMKII) and MAPK-activated protein kinase 2 (MAPKAPK2; Davis *et al.*, 2000) and was found to regulate many facets of neuronal functioning, including neuronal excitation, growth and survival, development and regeneration, circadian entrainment and long-term synaptic plasticity (reviewed by Lonze and Ginty, 2002; Borlikova and Endo, 2009). In rat cortical cells, an H_3 receptor antagonist was found to alleviate NMDA-induced neurotoxicity by activating the cAMP/PKA pathway, which subsequently facilitated GABA release (Dai *et al.*, 2007). It is well known that the signalling pathway of PKA/CREB has an anti-apoptotic effect (Lonze *et al.*, 2002; Ao *et al.*, 2006), and there is experimental evidence suggesting that CREB is actively involved in supporting neuroprotection (Lee *et al.*, 2005, 2009; Kim *et al.*, 2011; reviewed by Sakamoto *et al.*, 2011) and that its disruption in the brain leads to neurodegeneration (Lee *et al.*, 2002); thus, supporting a

pivotal role for CREB in preventing neuronal death (reviewed by Ferrer, 2002). In transgenic mice, the gene profiling of degenerating hippocampal tissue with electron microscopy reveals that the sustained inhibition of CREB function is associated with neuron degeneration, whereas its strong chronic activation primarily causes excitotoxic hippocampal cell death and inflammation, indicating that a fine tuned control of CREB expression is critical for the viability of pyramidal neurons (Valor *et al*., 2010). Altered expression of CREB and ICER (inducible cAMP early repressor), an endogenous CREB antagonist, and their possible alteration of GABA receptor subunits in various epileptic models suggest a definitive role for the PKA/CREB pathway in epileptogenesis (reviewed by Borlikova and Endo, 2009; Brooks-Kayal *et al*., 2009). On the other hand, a number of experimental (Lee *et al*., 2007; Zhu *et al*., 2012) and clinical (Park *et al*., 2003; Rakhade *et al*., 2005) findings appear, in some respects, to contradict the established neuroprotective role of this pathway as they indicate that an increased expression of CREB is associated with seizure-induced pathological alterations in the CNS. Therefore, further studies with H_3 receptor ligands are needed to elucidate the possible role of this particular pathway in epilepsy and the subsequent pathological remodelling of the hippocampus.

Activation of the MAPK pathway

G-protein-coupled activation of the MAPK pathway involves the Ras/Raf/MEK (MAP/ERK kinase) pathway that results in the phosphorylation of ERK1/2s. Activated ERKs phosphorylate several substrates, for example MAPK-activated protein kinases (MAPKAPKs; Wada and Penninger, 2004), of which MAPKAPK2 is associated with Akt phosphorylation (Rane *et al*., 2001). However, the occurrence of such cross-talk in the H_3 receptor pathways remains to be further examined, as H_3 receptor-mediated phosphorylation of Akt was observed to be independent of MAPK pathway in transfected SK-N-MC cells (Bongers *et al*., 2007b).

Notably, different components of the MAPK family are known to have opposing effects; the ERK/MAPK pathway is deemed to be pro-survival (Karmarkar *et al*., 2011), whereas the p38/MAPK and SAPK/JNK pathways are often implicated in cell death (de Lemos *et al*., 2010). More importantly, inhibition of ERK1/2 activation increases epileptiform activity and animal mortality in the pilocarpine model of status epilepticus (Berkeley *et al*., 2002) and ERK1/2 activation is thought to play a pivotal role in neuronal survival following hypoxic injury (Jin *et al*., 2002). Although the results of these studies indicated that ERK1/2 has a neuroprotective role, other studies have suggested ERK1/2 signalling has a detrimental role in neurotoxic responses (reviewed by Subramaniam and Unsicker, 2010). The role of ERK1/2 in status epilepticus is further complicated by evidence indicating that ERK1/2 activation is epileptogenic (Merlo *et al*., 2004) and triggers epilepsy in mice by augmenting NMDA receptor (GluN2B) function (Nateri *et al*., 2007).

Earlier, phosphorylation of the MAPK pathway induced by activation of rat H_3 (H_{3A} isoform) receptors in receptor transfected COS 7 cells (Drutel *et al*., 2001) led to the discovery that the MAPK pathway is linked to H_3 receptors. However, in rat hippocampal CA3 pyramidal cells H_3 receptor activation was also shown to be coupled indirectly to ERK2 phosphorylation, as thioperamide failed to alter phospho-ERK levels (Giovannini *et al*., 2003). The relevance of this H_3 receptor signalling pathway in the aetiology of chronic epilepsies has yet to be ascertained.

Activation of the PI3K/Akt/GSK3β axis

H_3 receptor activation in transfected cells leads to the activation of PI3K pathways and the subsequent phosphorylation–activation of another ubiquitous signalling molecule, Akt (PKB, serine/threonine kinase), which phosphorylates at serine residue and thereby inhibits the action of GSK-3β (pGSK-$3\beta_{ser9}$; Bongers *et al*., 2007b), a constitutively active, τ kinase. Advances in the understanding of signal transduction in the CNS regulated by Akt have paved the way to study the implications of the PI3K/Akt/GSK-3β axis (Brazil *et al*., 2004; Chuang, 2005). Akt has been shown to play an important role in preventing excitotoxic apoptosis by acting as a regulatory gate, preventing JNK activation (Kim *et al*., 2002).

In the CNS, the Akt/GSK-3β axis has emerged as a potential target for various neurological disorders. Activation of GSK-3β (pGSK-$3\beta_{tyr216}$) promotes apoptosis in a wide variety of conditions, while its inhibition promotes cell survival (Rickle *et al*., 2004; Takashima, 2009). The role of H_3 receptor-mediated activation of Akt/GSK-3β in the brain is still under investigation, but dysregulation of GSK-3β is linked to several neurodegenerative conditions including AD and other neurological disorders (Rickle *et al*., 2004; Takashima, 2009). The pro-apoptotic effect of activated GSK-3β suggests a potential role for its inhibitors in protection against neuronal cell death (Eldar-Finkelman, 2002; Takashima, 2009). Inhibition of GSK-3β was found to be critical in imparting neuroprotection in various models of neurodegeneration (Chin *et al*., 2005; Rosa *et al*., 2008), including KA-induced neurotoxicity (Goodenough *et al*., 2004). Selective GSK-3β inhibitors were found to reduce the development of complications in models of TLE, by limiting the extent of neuronal damage associated with TLE, without affecting the EEG parameters of KA-induced seizures (Busceti *et al*., 2007; Luna-Medina *et al*., 2007). Moreover, inhibition of GSK-3β has also been implicated in the mechanism of action of AEDs like valproic acid (Qing *et al*., 2008), suggesting a possible role for GSK-3β in the pathophysiology of epilepsy.

The novel finding that stimulation of H_3 receptors triggers activation of the Akt/GSK-3β pathway and protects against NMDA-induced neurotoxicity, and that both are blocked by the H_3-antagonist thioperamide (Bongers *et al*., 2007b; Mariottini *et al*., 2009), is contradicted by an *in vivo* study where inhibition of H_3 receptors by the H_3-antagonist ABT-239 conferred neuroprotection by elevating hippocampal GSK-$3\beta_{ser9}$ levels, which resulted in reduction in τ-phosphorylation in an Alzheimer model in mice (Bitner *et al*., 2011). These experimental anomalies require further elucidation to delineate this H_3 receptor-linked pathway. Reducing neuronal death is an important therapeutic goal in the context of a number of neurodegenerative diseases including refractory epilepsies (Sloviter, 2011). Therefore, the emerging finding that H_3 receptors are coupled to GSK-3β throws up an exciting

avenue to explore a new therapeutic opportunity, if any, germane to TLE-induced neurodegeneration.

Activation of PLA_2

H_3 receptor-induced activation of $G_{i/o}$-proteins seems to stimulate PLA_2 to induce the release of AA (Rouleau *et al.*, 2002). Usually, activation of mammalian PLA_2 cleaves membrane phospholipids liberating two major fatty acids of brain, AA and docosahexaenoic acid. Under pathological conditions, these metabolites act as precursors for various inflammatory compounds, for example PAF, prostaglandins, leukotrienes and lipid peroxides, which are crucial in mediating the oxidative and inflammatory responses in CNS pathologies such as stroke, AD, PD and multiple sclerosis (Sun *et al.*, 2010). As PLA_2 inhibitors confer neuroprotection in KA-induced neurodegeneration of hippocampal slices (Farooqui *et al.*, 2004) and increased activity of this enzyme in the hippocampus is associated with human TLE (Gattaz *et al.*, 2011), it would be interesting to investigate the significance of this pathway in epileptogenic mechanisms further by employing H_3 receptor ligands.

Inhibition of the Na^+/H^+ exchanger

H_3 receptor activation leads to the inhibition of the Na^+/H^+ exchanger (NHE; Silver *et al.*, 2001) by an as yet unknown mechanism, although a direct interaction of $G\alpha_{i/o}$-proteins has been proposed (Bongers *et al.*, 2007a). Activation of the H_3 receptor was shown to diminish neuronal NHE activity, and this pathway is proposed as the mechanism by which the H_3 receptor inhibits the excessive release of noradrenaline during protracted myocardial ischaemia (Hashikawa-Hobara *et al.*, 2012).

The NHE is of profound importance as it maintains intracellular physiological pH by the extrusion of one intracellular H^+ in exchange for one extracellular Na^+ across the plasma membrane and thereby prevents neural acidosis, as the loss of NHE function is hypothesised to lower seizure threshold (Cox *et al.*, 1997). Earlier, the defective functioning or absence of the NHE1 gene was shown to contribute to the neuronal death in the brains of mutant mice with epilepsy (Cox *et al.*, 1997; Zhao *et al.*, 2005). In line with this, NHE is assumed to favourably regulate neuronal excitability and post-ictal recovery in different transgenic models (reviewed by Obara *et al.*, 2008). However, in contrast, several studies have obtained experimental findings indicating that inhibitors targeting NHE are of significant therapeutic value in epilepsy (reviewed by Ali *et al.*, 2008). In this context, the influence of H_3 receptor ligands on NHE and subsequent implications in epilepsy need to be assessed.

Modulation of $[Ca^{2+}]_i$

Neuronal H_3 receptor agonism decreases K^+-induced extracellular calcium inflow, probably by impairing voltage operated ion channel (Silver *et al.*, 2002; Seyedi *et al.*, 2005), and inhibits histamine synthesis through the AC/PKA (Gomez-Ramirez *et al.*, 2002) and CaMKII pathways (Torrent *et al.*, 2005; Moreno-Delgado *et al.*, 2009). Conversely, H_3 receptor agonists, acting on recombinantly expressed H_3 receptors, transiently mobilize calcium from intracellular depots (Bongers *et al.*, 2006). To complicate this further, the H_3 receptor antagonist clobenpropit was found to reverse NMDA-induced Ca^{2+} accumulation in rat cortical neurons (Dai *et al.*, 2007). Also, it has been reported that both PKA and CaMKII tend to regulate phosphorylation and hence activation of the histamine synthesizing enzyme, HDC. Depolarization–stimulation of histamine synthesis is mediated by calcium entry and subsequent calmodulin and CaMKII activation, although it is unlikely that PKA-dependent stimulation of histamine synthesis is linked to depolarization (Gomez-Ramirez *et al.*, 2002; Torrent *et al.*, 2005). Previously, it was reported that, in rat brain cortical slices containing histaminergic nerve endings, the prototypical H_3 receptor antagonist (now considered an inverse agonist) thioperamide stimulated histamine synthesis in a concentration-dependent manner (Gomez-Ramirez *et al.*, 2002). These effects of thioperamide were mimicked by clobenpropit and A331440 (Moreno-Delgado *et al.*, 2006).

Neuronal Ca^{2+} homeostasis and Ca^{2+} signalling via CaMKII regulate neuronal well-being. Ca^{2+} dyshomeostasis due to inhibition of CaMKII results in aberrant calcium and glutamate signalling, which can lead to neurodegenerative diseases including glutamate excitotoxicity and epilepsy (Ashpole *et al.*, 2012). The implications of H_3 receptor-mediated alteration in neuronal $[Ca^{2+}]_i$ level pertaining to epileptogenesis still need to be elucidated.

Epilepsy and histamine H_3 receptors

The possibility that the brain histaminergic system is involved in epilepsy is being driven by plethora of experimental and clinical findings suggesting that histamine acts as an antiepileptic neurotransmitter. Activation of the central histaminergic system increases seizure threshold and decreases seizure susceptibility in electrically and chemically induced seizures and kindling mediated by histamine H_1 receptors (Tuomisto and Tacke, 1986; Tuomisto *et al.*, 1987; Yokoyama *et al.*, 1992; Iinuma *et al.*, 1993; Kamei *et al.*, 1998; Chen *et al.*, 2003; Hirai *et al.*, 2004; Ishikawa *et al.*, 2007; Nishida *et al.*, 2007; Zhu *et al.*, 2007). In addition, high doses of several centrally acting H_1 receptor antagonists when used as anti-allergic drugs occasionally induce convulsions in clinical settings (Yokoyama *et al.*, 1993b; Jang *et al.*, 2010; Takano *et al.*, 2010; Miyata *et al.*, 2011) and experimental models (Yokoyama *et al.*, 1993a, 1996; Kamei *et al.*, 2000; Singh and Goel, 2010), further supporting an association between the neuronal histaminergic system and epileptic seizure pathophysiology.

The involvement of histamine H_3 receptors in epilepsy is currently under investigation. The pharmacological properties of H_3 antagonists/inverse agonists with respect to their anticonvulsive potential has begun to receive increased attention, as mounting experimental evidence from both acute and chronic models of epilepsy indicate the effectiveness of

H_3 receptor antagonists. They were found to protect against experimental convulsions by increasing the release of histamine in the brain, which in turn interacts with H_1 receptors (Yokoyama *et al*., 1993c; 1994; Kakinoki *et al*., 1998; Ishizawa *et al*., 2000; Vohora *et al*., 2000; 2001; Chen *et al*., 2002). In addition, they are assumed to mediate their anticonvulsive action by several other mechanisms (Table 1), such as facilitation of GABA release (Ishizawa *et al*., 2000; Vohora *et al*., 2001; Zhang *et al*., 2003a,b), increasing histidine decarboxylase (HDC) activity (Yokoyama *et al*., 1994; Hirai *et al*., 2004) and synergism with AEDs (Ishizawa *et al*., 2000; Vohora *et al*., 2001; Uma Devi *et al*., 2011). Buoyed by encouraging results in experimental epilepsy, many academic and industrial units have begun extensive research to increase the efficacy of possible H_3 antagonists in clinical epilepsy. So far, the only success is in the form of pitolisant, which has progressed to phase II of a clinical trial for patients suffering from photosensitive epilepsy, a rare form of the disease where seizures are evoked by photic stimuli. The compound at a dose range of 20–60 mg, when administered alone as well as in combination with AEDs, dose-dependently improved the photoparoxysomal response. The onset of action was1–2 h post application and appreciably lasted from 8 h up to 36 h. Further progress in this direction has not emerged. (Tiligada *et al*., 2009; Kuhne *et al*., 2011).

By contrast, conflicting results have been published on the role of H_3 receptors (either induce seizure or mainly have no effect) in various models of experimental convulsions (Scherkl *et al*., 1991; Sturman *et al*., 1994; Wada *et al*., 1996; Fischer and van der Goot, 1998). These paradoxes could be suggestive of the involvement of non-histaminergic mechanisms for the epileptic disposition in the model studied. All this notwithstanding, it is proposed that the intrinsic histaminergic system exerts a powerful inhibitory function during epileptic seizure episodes, evidently via an H_1- and H_3-dependent mechanism. In line with this, H_3 receptor antagonists can be of therapeutic value in epilepsy, or at least a viable approach that can be combined with AEDs, especially in patients who are refractory or non-responsive to conventional therapies.

Histamine H_3 receptor and neuroprotection

The status of the histaminergic system with regard to its neuroprotective role is still vague and inconclusive. The importance of histamine in neuroprotection is illustrated by the association of brain histamine levels with seizure threshold and duration (Yawata *et al*., 2004) and the ability of histaminergic neurons to protect the developing hippocampus from KA-induced neuronal damage, which is partly mediated by H_1 and H_3 receptors (Kukko-Lukjanov *et al*., 2006; 2012). Likewise, KA-induced neurotoxicity was aggravated in mice treated with an H_1-receptor antagonist (Kukko-Lukjanov *et al*., 2010). At present, there is very little information regarding the effect of H_3 antagonists on neuronal survival and function. A role for histamine H_3 receptors in various neurodegenerative diseases, such as AD and PD, has been suggested (Alguacil and Pérez-García, 2003; Gemkow *et al*., 2009).

Numerous experimental findings have shown that histamine confers neuroprotection in degenerative changes due to ischaemia. For example, middle cerebral artery occlusion in the rat induces a long-lasting increase in neuronal histamine release in the striatum (Adachi *et al*., 1992). Moreover, histamine depletion with α-fluoromethylhistidine, an inhibitor of histidine decarboxylase (its synthesizing enzyme), significantly increases the number of necrotic pyramidal cells in the hippocampal CA1 region in rats subjected to cerebral ischaemia (Adachi *et al*., 1993). Post-infarction loading with histidine, a precursor of histamine, decreases the amount of neuronal damage in the rat brain (Adachi *et al*., 2005). In cultured cortical neurons, histamine protects against NMDA-induced necrosis via the histamine H_2 receptor (Dai *et al*., 2006).

Unlike the anticonvulsive role attributed to H_3 receptors in several studies, relatively little attention has been paid to their possible neuroprotective role especially in seizure-associated neurotoxicity. H_3 receptor-dependent modulation of neuroprotective mechanisms has also been demonstrated in diverse studies. A robust up-regulation of H_3 receptor mRNA was observed in certain brain areas that participate in epileptogenic processes after KA-induced seizures, indicative of a modulatory role of H_3 receptors (Lintunen *et al*., 2005) as well as during experimental ischaemia (Lozada *et al*., 2005). Increased H_3 receptor expression and subsequent constitutive activation of the downstream Akt/GSK-3β pathway could be the mechanism by which the H_3 receptor exerts its endogenous neuroprotective role (Bongers *et al*., 2007b). On the flip side and in line with an antiepileptic mechanism, H_3 receptor agonism aggravated delayed neuronal death in a rat model of cerebral ischaemia (Adachi *et al*., 1993). Moreover, H_3 receptor antagonism conferred neuroprotection by elevating the hippocampal GSK-$3\beta_{ser9}$ level, which resulted in a reduction in τ phosphorylation in an Alzheimer model in mice (Bitner *et al*., 2011). Physiological chaperons like heat shock proteins, HSPs (HSP 27 and 70) are up-regulated in various neurodegenerative conditions including epilepsy, but their exact role is as yet uncertain as they may have a protective mechanism, but they have also been linked to deleterious effects (reviewed in Turturici *et al*., 2011). An H_3 receptor antagonist was found to provide neuroprotection arising from their interaction with HSPs in a KA-induced neurotoxic model in teleost (Giusi *et al*., 2008).

The role of H_3 receptor ligands in neuroprotection is further confounded by a number of discrepancies that have emerged (Table 2). H_3 receptor antagonists have been found to be ineffective (Kukko-Lukjanov *et al*., 2006; Bongers *et al*., 2007b; Molina-Hernández and Velasco, 2008; Mariottini *et al*., 2009), and to reverse H_3 receptor agonists-mediated neuroprotective parameters (Shen *et al*., 2007; Fu *et al*., 2008) in various models of neurodegeneration. Furthermore, a short lasting but very high up-regulation of the expression of mRNA for all of the H_3 receptor isoforms (particularly H_{3A+D}) was observed in the areas most vulnerable to the excitotoxic effect of KA (in CA1 and CA3), which correlated well with neuronal damage (Jin *et al*., 2005; Lintunen *et al*., 2005), suggestive of a dual role for this receptor. Neurodegeneration could occur by the activation of H_{3A} receptor-mediated neuronal death through JNK pathways. However, this upregulation of H_{3A} receptor could be a compensatory rise to carry out

Table 1

H_3 recepor ligands and the mechanisms entailed in their antiepileptic effect in diverse models of epilepsy

H_3 receptor ligands	Model used	Effect observed	Mechanism	Reference
Thioperamide (3.75, 7.5 and 15 mg·kg^{-1} i.p.)	MES seizure in mice	↓ Duration of each phase of convulsion	H_3 antagonism/inverse agonism: reversal of auto-inhibitory HA synthesis and release; H_1-mediated seizure inhibition	Yokoyama *et al.*, 1993c
Clobenpropit (0.1, 0.3, 1 and 3 mg·kg^{-1} i.p.)	MES seizure in mice	↓ Duration of each phase of convulsion	As first mechanism; ↑ HDC activity	Yokoyama *et al.*, 1994
AQ-0145	MES seizure in mice	↓ Duration of each phase of convulsion	As first mechanism	Murakami *et al.*, 1995
Thioperamide (7.5 and 15 mg·kg^{-1} i.p.)	Proconvulsive effect of theophylline on MES seizure in mice	↓ Mortality	As first mechanism	Yokoyama *et al.*, 1997
Clobenpropit (20–40 mg·kg^{-1} i.p.)	MES- and PTZ-induced seizure in mice	↑ Threshold for tonic seizure in MES test ⊗ PTZ seizure threshold	As first mechanism; pharmacokinetic synergism with AEDs	Fischer and van der Goot, 1998
Thioperamide (5–10 mg·kg^{-1} i.p.) and Clobenpropit (1, 5, 10 and 50 μg i.c.v.)	Amygdaloid kindled (electrically) rats	↓ Seizure stage; ↓ AD duration	As first mechanism	Kakinoki *et al.*, 1998
Clobenpropit (0.5, 2, 5, and 10 mg·kg^{-1} i.p.)	Amygdaloid kindled (electrically) rats	↓ Seizure stage; ↓ AD duration	As first mechanism; interaction with GABA actions	Ishizawa *et al.*, 2000
Thioperamide (3.75, 7.5 and 15 mg·kg^{-1} i.p.) R-α-methylhistamine (10 μg i.c.v.)	PTZ-induced seizure in mice	↑ Latency of myoclonic jerks & clonic generalized seizures; ↓ % incidence; H_3 agonism reversed the above	As first mechanism;	Vohora *et al.*, 2000
Thioperamide and AQ 0145 (each 5 and 10 mg·kg^{-1} i.p. and 10–50 μg i.c.v.)	Amygdaloid kindled (electrically) rats	↓ Seizure stage; ↓ AD duration	As first mechanism	Kamei, 2001
Thioperamide (3.75–7.5 mg·kg^{-1} i.p.); *R*-α-methylhistamine (10 μg i.c.v.)	MES- and PTZ-induced seizure in mice	↑ Latency of myoclonic jerks and clonic generalized seizures; ↓ Duration of tonic and clonic phases; H_3 agonism reversed the above	As first mechanism; potentiation of AEDs	Vohora *et al.*, 2001
Thioperamide (5, 10 and 20 μg; i.c.v.)	PTZ-induced kindling in rats	↓ Duration of each phase of convulsion; ↑ seizure threshold	As first mechanism	Chen *et al.*, 2002
Clobenpropit (10 and 20 μg i.c.v.) Immepip (5 and 10 μg i.c.v.)	PTZ-induced kindling in rats	Delayed onset of kindling; ↑ latency of seizure stage; H_3 agonism reversed the above	As first mechanism	Zhang *et al.*, 2003a,b
Carcinine and Thioperamide (each 2–20 mg·kg^{-1} i.p.)	PTZ induced kindling in mice	↑ Latency of seizures; ↓ Seizure stages	↑ HDC activity; ↑ HA release	Chen *et al.*, 2004
Iodophenpropit, Clobenpropit, Thioperamide (each 10 mg·kg^{-1} i.p./i.c.v.), AQ0145 (20 mg·kg^{-1} i.p.); VUF5514, VUF5515 VUF4929 (i.c.v.)	Amygdaloid kindled (electrically) rats; MES seizure in rats	↓ Seizure stages; ↓ AD duration; ↓ tonic seizure ⊗ Duration of clonic phase	As first mechanism	Harada *et al.*, 2004a,b

Table 1

Continued

H_3 receptor ligands	Model used	Effect observed	Mechanism	Reference
Thioperamide (25 mg·kg^{-1} i.p.)	EL mice (model of human TLE)	↑ Latency; ↓ % of seizure incidence	↑ HDC activity; ↑ Brain HA release	Yawata *et al.*, 2004
Clobenpropit (i.c.v.)	PTZ-induced kindling in mice	↑ Latency of myoclonic jerks and clonic generalized seizures; ↓ Seizure stages	As first mechanism	Zhang *et al.*, 2004
Thioperamide (10, 20 and 50 μg i.c.v.)	Imipramine-induced seizures in amygdaloid kindle (electrically) rats	↓ Behavioural seizure; ↓ EEG seizure	As first mechanism	Ago *et al.*, 2006
Clobenpropit (0.75 and 1.5 mg·kg^{-1} i.p.)	MES seizure in mice	Inhibition of seizure	Pharmacodynamic synergism with pyridoxine	Uma Devi *et al.*, 2011
Thioperamide (2–10 mg·kg^{-1} i.p.) and *R*-α-methylhistamine (10–40 mg·kg^{-1} i.p.)	MES and PTZ induced seizure in mice	⊗ Seizure threshold in both model	H_3 antagonism and agonism	Scherkl *et al.*, 1991
Thioperamide and Burimamide	Picrotoxin induced seizure	↑ Severity of clonic convulsions	H_3 antagonism	Sturman *et al.*, 1994
Thiopermide (20 and 30 mg·kg^{-1} i.p.) Betahistine (200 and 400 mg·kg^{-1} i.p.)	Amygdaloid kindled rats	No anticonvulsive effect; mild effect only at very high dose	H_3 antagonism	Yoshida *et al.*, 2000
Thioperamide (15 mg·kg^{-1} i.p.)	Methionine-sulfoximine induced convulsion in mice	⊗ Seizure latency and mortality	H_3 antagonism	Vohora *et al.*, 2010

AD, after discharge; MES, Maximal electroshock; PTZ, pentylenetetrazole; ↑ increase; ↓ decrease; ⊗ no change.

regenerative/cell survival process via H_{3A}-coupled Ras-Raf-MEK pathways (Jin *et al.*, 2005; Lintunen *et al.*, 2005). Neurotoxic insult by 3-nitropropionic acid (3-NP) resulted in increased transcriptional activities of H_3 receptors, which was comparable with deleterious neuronal effects in rat and hamster (Canonaco *et al.*, 2005). In summary, H_3 receptor antagonism cannot be deemed to be neuroprotective until the confounding factors, such as phenotype and isoforms specific variations among the different experimental paradigms used, are taken into consideration. Hence, it would be interesting to explore the modulatory effect, if any, of H_3 receptor antagonists on the neurodegenerative processes associated with epilepsy.

Way ahead

The rapid increase in our understanding of the range and mode of operation of different neurotransmitter systems and of synaptic neurophysiology is leading to landmark advancement in the treatment of epilepsy with the advent of new AEDs. However, improvement in terms of clinical outcome has fallen short of expectations, with up to one-third of patients continuing to experience seizures or unacceptable medication-related side effects in spite of efforts to identify optimal treatment regimes with one or more drugs. A plethora of experimental findings lend credence to the anticonvulsive and neuroprotective effects of H_3 receptor ligands and they are currently in advanced stages of clinical development for a broad spectrum of central diseases (e.g. narcolepsy, AD, epilepsy and schizophrenia). As per the literature in hand, in spite of several experimental findings explicitly indicating an important role for central H_3 receptors in the inhibition of seizures, the development of hH_3 receptor ligands has been disappointingly slow, at least partly because of problems with selectivity. The only success met so far is in the form of pitolisant, which has reached phase II trial for photosensitive epilepsy. Nonetheless, the experimental findings accumulated in support of the involvement of H_3 receptors in epilepsy and concomitant neurodegeneration should not be discounted.

On the basis of the present data, the following key points can be taken into consideration to absolve the discrepancies observed and hence to bridge the gap between experimental findings and success in clinical settings.

- Averting the precipitation of status epilepticus is considered the most effective way to minimize neurodegeneration (Walker, 2007) and employment of immediate neuroprotective strategies could prevent epileptogenic changes (Acharya *et al.*, 2008). Intriguingly, H_3 receptor antagonists appear to possess both anticonvulsive and neuroprotective and/or disease modifying activity as suggested in numerous experimental findings. Strategically, a highly localized CNS

Table 2

H_3 receptor ligands and the mechanisms entailed in neuroprotective effect in diverse models of neurotoxicity

H_3 receptor ligands	Model used	Effect observed	Mechanism	Reference
Thioperamide (40–400 mg·kg^{-1} i.p.)	Ibotenate-induced brain lesion in IL-9-treated mice	↓ Brain lesion	H_3 antagonism/inverse agonism	Patkai *et al.*, 2001
Thioperamide (10^{-8}–10^{-5} M)	HA-induced neurotoxicity in cultured rat cerebellar granular neurons	↓ % of cell death	As 1st mechanism	Gepdiremen *et al.*, 2003
Thioperamide (10 mg·kg^{-1} i.p.)	3-NP-induced neurotoxicity in hamster	↑ H_1R mRNA, ↓ Motor behaviour	As 1st mechanism	Canonaco *et al.*, 2005
Thioperamide (10^{-7}–10^{-5} M)	NMDA-induced neurotoxicity in cultured rat cortical neurons	↓ NMDA-induced necrosis, ↑ Neuronal viability	As 1st mechanism, ↑ GABA release	Dai *et al.*, 2006
Thioperamide (1, 10, 10^2 & 10^3 nM) Clobenpropit (10, 10^2, 10^3 & 5000 nM)	KA-induced neurotoxicity in cultured rat hippocampal slices	↓ Neuronal degeneration, Clobenpropit had no effect	As 1st mechanism	Kukko-Lukjanov *et al.*, 2006
Clobenpropit (10^{-11}–10^{-7} M)	NMDA-induced neurotoxicity in cultured rat cortical neurons	↓ NMDA-induced necrosis, ↑ Neuronal viability	As 1st mechanism; Activation of cAMP/PKA pathway; ↑ GABA release, ↓ $[Ca^{2+}]_i$	Dai *et al.*, 2007
Thioperamide (10 mg·kg^{-1} i.p.)	Pb-induced neurotoxicity in teleost (*T. pavo*)	↓ Behavioural hyperactivity, ↓ Neurodegeneration, ↓ mRNA expression of HSPs (70 and 90)	Cross-talk between H_3R with HSPs	Giusi *et al.*, 2008
GSK 189254 (0.3 mg·kg^{-1} p.o.)	GSK 189254-treated rats	↑ Survival of dentate gyrus neurons	↑ NCAM-PSA expression	Foley *et al.*, 2009
ABT-239 (0.03, 0.1, 0.7, 1 mg·kg^{-1} i.p.)	Tg2576 and TAPP transgenic AD mice	↑ p-CREB, ↑ p-GSK3β_{ser9}, ↓ Tau hyperphosphorylation	As 1st mechanism	Bitner *et al.*, 2011
Thioperamide (10^{-4}& 10^{-4} M·L^{-1})	NMDA-induced neurotoxicity in rat PC12 cells	Reversal of carnosine induced neuroprotective effect and inhibition of glutamate release	As 1st mechanism	Shen *et al.*, 2007
Thioperamide (10 μM·L^{-1}) Clobenpropit (100 μM·L^{-1})	SK-N-MC cells transfected with *h*H_3R; Cultured rat cortical neurons and striatal slices	↑ cAMP accumulation, ↓ pAkt$_{Ser473}$, ↓ p-GSK3β_{Ser9}	As 1st mechanism	Bongers *et al.*, 2007b
Thioperamide (1 μM)	Cultured rat cortical stem cells	⊗ Cell proliferation and differentiation	As 1st mechanism	Molina-Hernández and Velasco, 2008
Thioperamide & Clobenpropit	A beta-42 induced neurotoxic rat PC12 cells	↓ Cell viability; reversal of inhibition of glutamate release	As 1st mechanism	Fu *et al.*, 2008
Thioperamide (10 μM·L^{-1}) Immepip (10 nM·L^{-1})	NMDA-induced neurotoxicity in cultured mouse cortical neurons	Blockade of H_3 agonist induced- ↑ pAkt$_{Ser473}$, ↑ Bcl-2 expression, ↓ LDH, GSK-3β and caspase 3 activity; ⊗ *per se* on the above	As 1st mechanism	Mariottini *et al.*, 2009
–	KA in SD rats	Possible anti-seizure, neuroprotective role	Brief ↓ H_{3A+D} mRNA (24 h); ↑↑ H_{3A+D} mRNA (after 1 week)	Jin *et al.*, 2005
–	KA in SD rats	Variable (site & time dependent)- Both anti- and/or seizurogenicity; from neuronal death to survival/regeneration	Transient expression of- ↑↑ H_{3A+D} mRNA followed by ↓ H_{3A+D} mRNA	Lintunen *et al.*, 2005

LDH, lactate dehydrogenase; pAkt$_{Ser473}$, phosphorylation of Akt at serine 473 residue; p-GSK3β_{ser9}, phosphorylation of GSK-3β at serine 9 residue; NCAM-PSA, neural cell adhesion molecule-polysialylation; PC-12, pheochromocytoma cell line; SK-N-MC, a human neuroblastoma cell line that stably expresses the human H_3R; SD, Sprague–Dawley; ↑ increase; ↑↑ very high increase; ↓ decrease; – no H_3R ligand used; ⊗ no change.

expression of H_3 receptors (Drutel *et al.*, 2001) is likely to minimize peripheral side effects, making them a promising target for epilepsy and neurotoxicity.

- The intrinsic activity of H_3 receptor inverse agonists that reverse constitutive suppression of histamine and/or GABA release (Morisset *et al.*, 2000; Dai *et al.*, 2007) could contribute to but is unlikely to fully account for receptor-dependent seizure suppression and neuroprotection. The beneficial effects of some H_3 antagonists observed could also be mediated through a non-histaminergic mechanism (Uma Devi *et al.*, 2011). Hence, further investigations are warranted to reveal cross-talk with other cellular factors (Giusi *et al.*, 2008; Moreno *et al.*, 2011).
- An explanation for H_3 receptors being associated with the dual role of both cell death and survival could be the coupling of this receptor to MAPK pathways, different components of which can play an opposing role (Wada and Penninger, 2004). Moreover, ERK1/2 activation may initially defy oxidative damage, but prolonged oxidative stress leads to exhaustion of cellular defences and it serves as a signal to trigger cell death (Luo and DeFranco, 2006). Again, there are findings that indicate that H_3 receptor agonism *in vitro* (Bongers *et al.*, 2007b) leads to signalling changes in the Akt/GSK-3β pathway analogous to those observed with H_3 receptor antagonism *in vivo* (Bitner *et al.*, 2011). This paradox could be attributed to the possible phenotypic variation in the signalling pathways between the two experimental systems used. Hence, improved understanding of the signal transduction cascades that are activated by the H_3 receptor is essential in order to elucidate the molecular mechanisms underlying the potential H_3 receptor-mediated modulation of brain function. The neurotoxicity observed in the presence of high levels of histamine may be due to the interaction of the convulsant with other neurotransmitter receptors and/or other pathways (Díaz-Trelles *et al.*, 1999).
- Both H_3 agonism and antagonism have been found to attenuate Ca^{2+} influx and $[Ca^{2+}]_i$ levels. The possible explanation for these inconsistencies in H_3 receptor-mediated Ca^{2+} signalling is speculated to be due to the presence of different ligand-bound active state conformations that couple differentially to the signalling system (Seyedi *et al.*, 2005; Dai *et al.*, 2007). A change in cell membrane composition, as in *Apoe*$^{-/-}$ mice, could also affect the structural conformation of H_3 receptors and hence alter its ligand binding characteristics (van Meer *et al.*, 2007).
- Due to the advent of powerful tools like genetic engineering, the existence of more than 20 different species-distinct splice variants of H_3 receptor have been identified, generating large molecular heterogeneity (reviewed in Hancock *et al.*, 2003; Leurs *et al.*, 2011). The resultant functional consequences with respect to their different CNS distribution patterns, biased ligand binding and their clinical relevance have yet to be determined. The dichotomous role of H_3 receptors as demonstrated by the transient and variable expression of various H_3 receptor isoforms in different brain regions that correlated with both neuronal survival and death in KA-treated rats (Jin *et al.*, 2005; Lintunen *et al.*, 2005) could be attributed to the existence of its pharmacological variants.
- In addition, it is anticipated that the interaction of histamine receptors with the intracellular transduction pathways is evidently not straightforward. The complexity arisen from the emergence of various functional isoforms differentially coupled to various G-proteins, the possible intertwining of signalling pathways (Drutel *et al.*, 2001) and interaction with other neurotransmitter receptors and/or pathways (Díaz-Trelles *et al.*, 1999) must be taken into account by selective pharmacological targeting, possibly by devising isoform-specific ligands.
- On the basis of the substantial experimental findings generated so far, H_3 receptor antagonists can be envisaged as having a therapeutic effect on epileptic and associated neurodegenerative disorders. An enhanced understanding of the mechanisms of seizure control and neuroprotective effects mediated via H_3 receptors in the light of the emerging signalling pathways coupled to it must be sought; as such mechanisms are likely to be the most valuable candidates for novel therapeutic interventions for improved seizure control. With that in mind, efforts should be taken to develop selective H_3 receptor agonists, antagonists and inverse agonists, which could provide the lead for the potential exploitation of the histaminergic system in the treatment of epilepsy and epileptogenesis.

Acknowledgement

This work was supported by assistance from University Grants Commission Special Assistance Programme (UGC-SAP) to D V and UGC- RGNF to M B.

Statement of conflict of interest

The authors declare no conflict of interest.

References

Acharya JN (2002). Recent advances in epileptogenesis. Curr Sci 82: 679–688.

Acharya MM, Hattiangady B, Shetty A (2008). Progress in neuroprotective strategies for preventing epilepsy. Prog Neurobiol 84: 363–404.

Adachi N (2005). Cerebral ischemia and brain histamine. Brain Res Rev 50: 275–286.

Adachi N, Itoh Y, Oishi R, Saeki K (1992). Direct evidence for increased continuous histamine release in the striatum of conscious freely moving rats produced by middle cerebral artery occlusion. J Cereb Blood Flow Metab 12: 477–483.

Adachi N, Oishi R, Itano Y, Yamada T, Hirakawa M, Saeki K (1993). Aggravation of ischemic neuronal damage in the rat hippocampus by impairment of histaminergic neurotransmission. Brain Res 602: 165–168.

Adachi N, Liu K, Arai T (2005). Prevention of brain infarction by postischemic administration of histidine in rats. Brain Res 1039: 220–223.

Ago J, Ishikawa T, Matsumoto N, Ashequr Rahman M, Kamei C (2006). Mechanism of imipramine-induced seizures in amygdala-kindled rats. Epilepsy Res 72: 1–9.

Alguacil LF, Pérez-García C (2003). Histamine H3 receptor: a potential drug target for the treatment of central nervous system disorders. Curr Drug Targets CNS Neurol Disord 2: 303–313.

Ali A, Ahmad FJ, Dua Y, Pillai KK, Vohora D (2008). Seizures and sodium hydrogen exchangers: potential of sodium hydrogen exchanger inhibitors as novel anticonvulsants. CNS Neurol Disord Drug Targets 7: 343–347.

Ao H, Ko SW, Zhuo M (2006). CREB activity maintains the survival of cingulate cortical pyramidal neurons in the adult mouse brain. Mol Pain 2: 15.

Arrang JM, Garbarg M, Schwartz JC (1983). Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature 302: 832–837.

Arrang JM, Morisset S, Gbahou F (2007). Constitutive activity of the histamine H_3 receptor. Trends Pharmacol Sci 28: 350–357.

Ashpole NM, Song W, Brustovetsky T, Engleman EA, Brustovetsky N, Cummins TR *et al*. (2012). Calcium/calmodulin-dependent protein kinase (CaMKII) inhibition induces neurotoxicity via dysregulation of glutamate/calcium signaling and hyperexcitability. J Biol Chem 287: 8495–8506.

Bakker RA, Lozada AF, van Marle A, Shenton FC, Drutel G, Karlstedt K *et al*. (2006). Discovery of naturally occurring splice variants of the rat histamine H3 receptor that act as dominant-negative isoforms. Mol Pharmacol 69: 1194–1206.

Berkeley JL, Decker MJ, Levey AI (2002). The role of muscarinic acetylcholine receptor-mediated activation of extracellular signal-regulated kinase 1/2 in pilocarpine-induced seizures. J Neurochem 82: 192–201.

Bitner RS, Markosyan S, Nikkel AL, Brioni JD (2011). In-vivo histamine H_3 receptor antagonism activates cellular signaling suggestive of symptomatic and disease modifying efficacy in Alzheimer's disease. Neuropharmacology 60: 460–466.

Bongers G, Sallmen T, Passani M, Mariottini C, Wendelin D, Lozada A *et al*. (2006). New signaling pathways for the histamine H3 receptor. In: *Proceedings of the XXXVth Annual Meeting of European Histamine Research Societ*.

Bongers G, Bakker RA, Leurs R (2007a). Molecular aspects of the histamine H_3 receptor. Biochem Pharmacol 73: 1195–1204.

Bongers G, Sallmen T, Passani MB, Mariottini C, Wendelin D, Lozada A *et al*. (2007b). The Akt/GSK-3beta axis as a new signaling pathway of the histamine H (3) receptor. J Neurochem 103: 248–258.

Borlikova G, Endo S (2009). Inducible cAMP early repressor (ICER) and brain functions. Mol Neurobiol 40: 73–86.

Brazil DP, Yang ZZ, Hemmings BA (2004). Advances in protein kinase B signalling: AKTion on multiple fronts. Trends Biochem Sci 29: 233–242.

Brooks-Kayal AR, Raol YH, Russek SJ (2009). Alteration of epileptogenesis genes. Neurother 6: 312–318.

Brown RE, Stevens DR, Haas HL (2001). The physiology of brain histamine. Prog Neurobiol 63: 637–672.

Busceti CL, Biagioni F, Aronica E, Riozzi B, Storto M, Battaglia G *et al*. (2007). Induction of the Wnt inhibitor, Dickkopf-1, is associated with neurodegeneration related to temporal lobe epilepsy. Epilepsia 48: 694–705.

Canonaco M, Madeo M, Alò R, Giusi G, Granata T, Carelli A *et al*. (2005). The histaminergic signaling system exerts a neuroprotective role against neurodegenerative-induced processes in the hamster. J Pharmacol Exp Ther 315: 188–195.

Chen Z, Li WD, Zhu LJ, Shen YJ, Wei EQ (2002). Effects of histidine, a precursor of histamine, on pentylenetetrazole-induced seizures in rats. Acta Pharmacol Sin 23: 361–366.

Chen Z, Li Z, Sakurai E, Izadi Mobarakeh J, Ohtsu H, Watanabe T *et al*. (2003). Chemical kindling induced by pentylenetetrazol in histamine H(1) receptor gene knockout mice (H(1)KO), histidine decarboxylase-deficient mice (HDC(-/-)) and mast cell-deficient W/W(v) mice. Brain Res 968: 162–166.

Chen Z, Sakurai E, Hu W, Jin C, Kiso Y, Kato M *et al*. (2004). Pharmacological effects of carcinine on histaminergic neurons in the brain. Br J Pharmacol 143: 573–580.

Chin PC, Majdzadeh N, D'Mello SR (2005). Inhibition of GSK-3β is a common event in neuroprotection by different survival factors. Mol Brain Res 137: 193–201.

Choi DW (1992). Excitotoxic cell death. J Neurobiol 23: 1267–1276.

Chuang DM (2005). The antiapoptotic actions of mood stabilizers: molecular mechanisms and therapeutic potentials. Ann N Y Acad Sci 1053: 195–204.

Clark EA, Hill SJ (1996). Sensitivity of histamine H3 receptor agonist-stimulated [^{35}S]GTPγS binding to pertussis toxin. Eur J Pharmacol 296: 223–225.

Connelly WM, Shenton FC, Lethbridge N, Leurs R, Waldvogel HJ, Faull RL *et al*. (2009). The histamine H4 receptor is functionally expressed on neurons in the mammalian CNS. Br J Pharmacol 157: 55–63.

Cox GA, Lutz CM, Yang CL, Biemesderfer D, Bronson RT, Fu A *et al*. (1997). Sodium/hydrogen exchanger gene defect in slow-wave epilepsy mutant mice Cell. Erratum in. Cell 91: 861.

Dai H, Zhang Z, Zhu Y, Shen Y, Hu W, Huang Y *et al*. (2006). Histamine protects against NMDA-induced necrosis in cultured cortical neurons through H2 receptor/cAMP/protein kinase A and H3 receptor/GABA release pathways. J Neurochem 96: 1390–1400.

Dai H, Fu Q, Shen Y, Hu W, Zhang Z, Timmerman H *et al*. (2007). The histamine H3 receptor antagonist clobenpropit enhances GABA release to protect against NMDA-induced excitotoxicity through the cAMP/protein kinase A pathway in cultured cortical neurons. Eur J Pharmacol 563: 117–123.

Davis S, Vanhoutte P, Pages C, Caboche J, Laroche S (2000). The MAPK/ERK cascade targets both Elk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus in vivo. J Neurosci 20: 4563–4572.

Díaz-Trelles R, Solana-López A, Fernández-González JR, Novelli A, Fernández-Sánchez MT (1999). Terfenadine induces toxicity in cultured cerebellar neurons: a role for glutamate receptors. Amino Acids 16: 59–70.

Dichter MA (2009). Emerging concepts in the pathogenesis of epilepsy and epileptogenesis. Arch Neurol 66: 443–447.

Drutel G, Peitsaro N, Karlstedt K, Wieland K, Smit MJ, Timmerman H *et al*. (2001). Identification of rat H_3 receptor isoforms with different brain expression and signaling properties. Mol Pharmacol 59: 1–8.

Eldar-Finkelman H (2002). Glycogen synthase kinase 3: an emerging therapeutic target. Trends Mol Med 8: 126–132.

Esbenshade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD (2008). The histamine H_3 receptor: an attractive target for the treatment of cognitive disorders. Br J Pharmacol 154: 1166–1181.

Farooqui AA, Ong WY, Horrocks LA (2004). Neuroprotection abilities of cytosolic phospholipase A2 inhibitors in kainic acid-induced neurodegeneration. Curr Drug Targets Cardiovasc Haematol Disord 4: 85–96.

Ferrer I (2002). Cell signaling in the epileptic hippocampus. Rev Neurol 34: 544–550.

Fischer W, van der Goot H (1998). Effect of clobenpropit, a centrally acting histamine H3-receptor antagonist on electroshock- and pentylenetetrazol-induced seizures in mice. J Neural Transm 105: 587–599.

Foley AG, Prendergast A, Barry C, Scully D, Upton N, Medhurst AD *et al*. (2009). H3 receptor antagonism enhances NCAM PSA-mediated plasticity and improves memory consolidation in odor discrimination and delayed match-to-position paradigms. Neuropsychopharmacology 34: 2585–2600.

Fox GB, Esbenshade TA, Pan JB, Radek RJ, Krueger KM, Yao BB *et al*. (2005). Pharmacological properties of ABT-239 [4-(2-{2-[(2R)-2-Methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H3 receptor antagonist. J Pharmacol Exp Ther 313: 176–190.

Fu Q, Dai H, Hu W, Fan Y, Shen Y, Zhang W *et al*. (2008). Carnosine protects against Abeta42-induced neurotoxicity in different rat PC12 cells. Cell Mol Neurobiol 28: 307–316.

Garbarg M, Schwartz JC (1985). Histamine receptors in the brain. N Engl Reg Allergy Proc 6: 195–200.

Gattaz WF, Valente KD, Raposo NR, Vincentiis S, Talib LL (2011). Increased PLA2 activity in the hippocampus of patients with temporal lobe epilepsy and psychosis. J Psychiatr Res 45: 1617–1620.

Gemkow MJ, Davenport AJ, Harich S, Ellenbroek BA, Cesura A, Hallett D (2009). The histamine H3 receptor as a therapeutic drug target for CNS disorders. Drug Discov Today 14: 509–515.

Gepdiremen A, Buyukokuroglu ME, Hacimuftuoglu A, Suleyman H (2003). Contribution of the histaminergic receptor subtypes to histamine-induced cerebellar granular neurotoxicity. Pol J Pharmacol 55: 383–388.

Giovannini MG, Efoudebe M, Passani MB, Baldi E, Bucherelli C, Giachi F *et al*. (2003). Improvement in fear memory by histamine-elicited ERK2 activation in hippocampal CA3 cells. J Neurosci 23: 9016–9023.

Giusi G, Alò R, Crudo M, Facciolo RM, Canonaco M (2008). Specific cerebral heat shock proteins and histamine receptor cross-talking mechanisms promote distinct lead-dependent neurotoxic responses in teleosts. Toxicol Appl Pharmacol 227: 248–256.

Gomez-Ramirez J, Ortiz J, Blanco I (2002). Presynaptic H_3 autoreceptors modulate histamine synthesis through cAMP pathway. Mol Pharmacol 6: 239–245.

Gonzalez GA, Montminy MR (1989). Cyclic AMP stimulates somatostatin gene transcription by phosphorylation of CREB at serine 133. Cell 59: 675–680.

Goodenough S, Conrad S, Skutella T, Behl C (2004). Inactivation of glycogen synthase kinase-3beta protects against kainic acid-induced neurotoxicity in vivo. Brain Res 1026: 116–125.

Haas HL, Sergeeva OA, Selbach O (2008). Histamine in the nervous system. Physiol Rev 88: 1183–1241.

Hancock AA, Esbenshade TA, Krueger KM, Yao BB (2003). Genetic and pharmacological aspects of histamine H3 receptor heterogeneity. Life Sci 73: 3043–3072.

Harada C, Fujii Y, Hirai T, Shinomiya K, Kamei C (2004a). Inhibitory effect of iodophenpropit, a selective histamine H3 antagonist, on amygdaloid kindled seizures. Brain Res Bull 63: 143–146.

Harada C, Hirai T, Fujii Y, Harusawa S, Kurihara T, Kamei C (2004b). Intracerebroventricular administration of histamine H3 receptor antagonists decreases seizures in rat models of epilepsia. Methods Find Exp Clin Pharmacol 26: 263–270.

Hashikawa-Hobara N, Chan NY, Levi R (2012). Histamine 3 receptor activation reduces the expression of neuronal angiotensin II type 1 receptorsin the heart. J Pharmacol Exp Ther 340: 185–191.

Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM *et al*. (1997). International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev 49: 253–278.

Hirai T, Okuma C, Harada C, Mio M, Ohtsu H, Watanabe T *et al*. (2004). Development of amygdaloid kindling in histidine decarboxylase deficient and histamine H1 receptor-deficient mice. Epilepsia 45: 309–313.

Iinuma K, Yokoyama H, Otsuki T, Yanai K, Watanabe T, Ido T *et al*. (1993). Histamine H1 receptors in complex partial seizures. Lancet 341: 238.

Ishikawa T, Takechi K, Rahman A, Ago J, Matsumoto N, Murakami A *et al*. (2007). Influences of histamine H_1 receptor antagonists on maximal electroshock seizure in infant rats. Biol Pharm Bull 30: 477–480.

Ishizawa K, Chen Z, Okuma C, Sugimoto Y, Fujii Y, Kamei C (2000). Participation of GABAergic and histaminergic systems in inhibiting amygdaloid kindled seizures. Jpn J Pharmacol 82: 48–53.

Jang DH, Manini AF, Trueger NS, Duque D, Nestor NB, Nelson LS *et al*. (2010). Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose. Clin Toxicol (Phila) 48: 945–948.

Jansen FP, Mochizuki T, Yamamoto Y, Timmerman H, Yamatodani A (1998). In vivo modulation of rat hypothalamic histamine release by the histamine H_3 receptor ligands, imepip and clobenpropit. Effects of intrahypothalamic and peripheral application. Eur J Pharmacol 362: 149–155.

Jin C, Lintunen M, Panula P (2005). Histamine H(1) and H(3) receptors in the rat thalamus and their modulation after systemic kainic acid administration. Exp Neurol 194: 43–56.

Jin CL, Zhuge ZB, Wu DC, Zhu YY, Wang S, Luo JH *et al*. (2007). Lesion of the tuberomammillary nucleus E2-region attenuates postictal seizure protection in rats. Epilepsy Res 73: 250–258.

Jin K, Mao XO, Zhu Y, Greenberg DA (2002). MEK and ERK protect hypoxic cortical neurons via phosphorylation of Bad. J Neurochem 80: 119–125.

Kakinoki H, Ishizawa K, Fukunaga M, Fujii Y, Kamei C (1998). The effects of histamine H3-receptor antagonists on amygdaloid kindled seizures in rats. Brain Res Bull 46: 461–465.

Kamei C (2001). Involvement of central histamine in amygdaloid kindled seizures in rats. Behav Brain Res 124: 243–250.

Kamei C, Ishizawa K, Kakinoki H, Fukunaga M (1998). Histaminergic mechanisms in amygdaloid-kindled seizures in rats. Epilepsy Res 30: 187–194.

Kamei C, Ohuchi M, Sugimoto Y, Okuma C (2000). Mechanism responsible for epileptogenic activity by first generation H1 antagonists in rats. Brain Res 887: 183–186.

Karmarkar SW, Bottum KM, Krager SL, Tischkau SA (2011). ERK/MAPK is essential for endogenous neuroprotection in SCN2.2 cells. Plos ONE 6: e23493.

Kim AH, Yano H, Cho H, Meyer D, Monks B, Margolis B *et al*. (2002). Akt1 regulates a JNK scaffold during excitotoxic apoptosis. Neuron 35: 697–709.

Kim BS, Kim MY, Leem YH (2011). Hippocampal neuronal death induced by kainic acid and restraint stress is suppressed by exercise. Neuroscience 194: 291–301.

Kiviranta T, Tuomisto L, Airaksinen EM (1995). Histamine in cerebrospinal fluid of children with febrile convulsions. Epilepsia 36: 276–280.

Kuhne S, Wijtmans M, Lim HD, Leurs R, de Esch IJ (2011). Several down, a few to go: histamine H_3 receptor ligands making the final push towards the market? Expert Opin Investig Drugs 20: 1629–1648.

Kukko-Lukjanov TK, Soin S, Taira T, Michelsen KA, Panula P, Holopainen IE (2006). Histaminergic neurons protect the developing hippocampus from kainic acid induced neuronal damage in an organotypic coculture system. J Neurosci 26: 1088–1097.

Kukko-Lukjanov TK, Lintunen M, Jalava N, Lauren HB, Lopez-Picon FR, Michelsen KA *et al*. (2010). Involvement of histamine 1 receptor in seizure susceptibility and neuroprotection in immature mice. Epilepsy Res 90: 8–15.

Kukko-Lukjanov TK, Grönman M, Lintunen M, Laurén HB, Michelsen KA, Panula P *et al*. (2012). Histamine 1 receptor knockout mice show age-dependent susceptibility to status epilepticus and consequent neuronal damage. Epilepsy Res 100: 80–92.

Lee B, Butcher GQ, Hoyt KR, Impey S, Obrietan K (2005). Activity-dependent neuroprotection and cAMP response element binding protein (CREB): kinase coupling, stimulus intensity, and temporal regulation of CREB phosphorylation at serine 133. J Neurosci 25: 1137–1148.

Lee B, Dziema H, Lee KH, Choi YS, Obrientan K (2007). CRE-mediated transcription and COX-2 expression in the pilocarpine model of status epilepticus. Neurobiol Dis 25: 80–91.

Lee B, Cao R, Choi YS, Cho HY, Rhee AD, Hah CK *et al*. (2009). The CREB/CRE transcriptional pathway: protection against oxidative stress-mediated neuronal cell death. J Neurochem 108: 1251–1265.

Lee JK, Choi SS, Lee HK, Han KJ, Han EJ, Suh HW (2002). Effects of MK-801 and CNQX on various neurotoxic responses induced by kainic acid in mice. Mol Cells 14: 339–347.

de Lemos L, Junyent F, Verdaguer E, Folch J, Romero R, Pallàs M *et al*. (2010). Differences in activation of ERK1/2 and p38 kinase in Jnk3 null mice following KA treatment. J Neurochem 114: 1315–1322.

Leurs R, Bakker RA, Timmerman H, de Esch IJ (2005). The histamine H3 receptor: from gene cloning to H_3 receptor drugs. Nat Rev Drug Discov 4: 107–120.

Leurs R, Chazot PL, Shenton FC, Lim HD, de Esch IJ (2009). Molecular and biochemical pharmacology of the histamine H4 receptor. Br J Pharmacol 157: 14–23.

Leurs R, Vischer HF, Wijtmans M, de Esch IJ (2011). En route to new blockbuster anti-histamines: surveying the offspring of the expanding histamine receptor family. Trends Pharmacol Sci 32: 250–257.

Lintunen M, Sallmen T, Karlstedt K, Panula P (2005). Transient changes in the limbic histaminergic system after systemic kainic acid-induced seizures. Neurobiol Dis 20: 155–169.

Lonze BE, Ginty DD (2002). Function and regulation of CREB family transcription factors in the nervous system. Neuron 35: 605–623.

Lonze BE, Riccio A, Cohen S, Ginty DD (2002). Apoptosis, axonal growth defects, and degeneration of peripheral neurons in mice lacking CREB. Neuron 34: 371–385.

Loscher W, Brandt C (2010). Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol Rev 62: 668–700.

Lovenberg TW, Roland BL, Wilson SJ, Jiang X, Pyati J, Huvar A *et al*. (1999). Cloning and functional expression of the human histamine H3 receptor. Mol Pharmacol 55: 1101–1107.

Lozada A, Munyao N, Sallmen T, Lintunen M, Leurs R, Lindsberg PJ *et al*. (2005). Postischemic regulation of central histamine receptors. Neuroscience 136: 371–379.

Luna-Medina R, Cortes-Canteli M, Sanchez-Galiano S, Morales-Garcia JA, Martinez A, Santos A *et al*. (2007). NP031112, a thiadiazolidinone compound, prevents inflammation and neurodegeneration under excitotoxic conditions: potential therapeutic role in brain disorders. J Neurosci 27: 5766–5776.

Luo Y, DeFranco DB (2006). Opposing roles for ERK1/2 in neuronal oxidative toxicity: distinct mechanisms of ERK1/2 action at early versus late phases of oxidative stress. J Biol Chem 281: 16436–16442.

Mariottini C, Scartabelli T, Bongers G, Arrigucci S, Nosi D, Leurs R *et al*. (2009). Activation of the histaminergic H_3 receptor induces phosphorylation of the Akt/GSK-3 beta pathway in cultured cortical neurons and protects against neurotoxic insults. J Neurochem 110: 1469–1478.

van Meer P, Pfankuch T, Raber J (2007). Reduced histamine levels and H3 receptor antagonist-induced histamine release in the amygdala of Apoe-/- mice. J Neurochem 103: 124–130.

Merlo D, Cifelli P, Cicconi S, Tancredi V, Avoli M (2004). 4-Aminopyridine-induced epileptogenesis depends on activation of mitogen-activated protein kinase ERK. J Neurochem 89: 654–659.

Miyata I, Saegusa H, Sakurai M (2011). Seizure-modifying potential of histamine H1 antagonists: a clinical observation. Pediatr Int 53: 706–708.

Molina-Hernández A, Velasco I (2008). Histamine induces neural stem cell proliferation and neuronal differentiation by activation of distinct histamine receptors. J Neurochem 106: 706–717.

Moreno E, Hoffmann H, Gonzalez-Sepúlveda M, Navarro G, Casadó V, Cortés A *et al*. (2011). Dopamine D1-histamine H3 receptor heteromers provide a selective link to MAPK signaling in GABAergic neurons of the direct striatal pathway. J Biol Chem 286: 5846–5854.

Moreno-Delgado D, Torrent A, GóMEZ-Ramírez J, de Esch I, Blanco I, Ortiz J (2006). Constitutive activity of H3 autoreceptors modulates histamine synthesis in rat brain through the cAMP/PKA pathway. Neuropharmacology 51: 517–523.

Moreno-Delgado D, GóMEZ-Ramírez J, Torrent-Moreno A, González-Sepúlveda M, Blanco I, Ortiz J (2009). Different role of cAMP dependent protein kinase and CaMKII in H3 receptor regulation of histamine synthesis and release. Neuroscience 164: 1244–1251.

Morisset S, Rouleau A, Ligneaux X, Gbahou F, Tardivel-Lacombe J, Stark H *et al*. (2000). High constitutive activity of native H3 receptors regulates histamine neurons in brain. Nature 408: 860–864.

Moya-Garcia AA, Medina MA, S'anchez-Jim'enez F (2005). Mammalian histidine decarboxylase: from structure to function. Bioessays 27: 57–63.

Murakami K, Yokoyama H, Onodera K, Iinuma K, Watanabe T (1995). AQ-0145, a newly developed histamine H3 antagonist, decreased seizure susceptibility of electrically induced convulsions in mice. Methods Find Exp Clin Pharmacol 17 (Suppl. C): 70–73.

Nateri AS, Raivich G, Gebhardt C, Da Costa C, Naumann H, Vreugdenhil M *et al*. (2007). ERK activation causes epilepsy by stimulating NMDA receptor activity. EMBO J 26: 4891–4901.

Naylor DE (2010). Glutamate and GABA in the balance: convergent pathways sustain seizures during status epilepticus. Epilepsia 51 (Suppl. 3): 106–109.

Nishida N, Huang ZL, Mikuni N, Miura Y, Urade Y, Hashimoto N (2007). Deep brain stimulation of the posterior hypothalamus activates the histaminergic system to exert antiepileptic effect in rat Pentylenetetrazole model. Exp Neurol 205: 132–144.

Nuutinen S, Panula P (2010). Histamine in neurotransmission and brain diseases. Adv Exp Med Biol 709: 95–107.

Obara M, Szeliga M, Albrecht J (2008). Regulation of pH in the mammalian central nervous system under normal and pathological conditions: facts and hypotheses. Neurochem Int 52: 905–919.

Oda T, Matsumoto S (2001). [Identification and characterization of histamine H4 receptor]. Nihon Yakurigaku Zasshi 118: 36–42. [Article in Japanese].

Okakura K, Yamatodani A, Mochizuki T, Horii A, Wada H (1992). Glutamatergic regulation of histamine release from rat hypothalamus. Eur J Pharmacol 213: 189–192.

Okakura-Mochizuki K, Mochizuki T, Yamamoto Y, Horii A, Yamatodani A (1996). Endogenous GABA modulates histamine release from the anterior hypothalamus. J Neurochem 67: 171–176.

Panula P, Yang HY, Costa E (1984). Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci U S A 81: 2572–2576.

Panula P, Airaksinen MS, Pirvola U, Kotilainen E (1990). A histamine containing neuronal system in human brain. Neuroscience 34: 127–132.

Park SA, Kim TS, Choi KS, Park HJ, Heo K, Lee BI (2003). Chronic activation of CREB and p90RSK in human epileptic hippocampus. Exp Mol Med 35: 365–370.

Parsons ME, Ganellin CR (2006). Histamine and its receptors. Br J Pharmacol 147 (Suppl. 1): S127–S135.

Passani MB, Blandina P (2011). Histamine receptors in the CNS as targets for therapeutic intervention. Trends Pharmacol Sci 32: 242–249.

Passani MB, Giannoni P, Bucherelli C, Baldi E, Blandina P (2007). Histamine in the brain: beyond sleep and memory. Biochem Pharmacol 73: 1113–1122.

Patkai J, Mesples B, Dommergues MA, Fromont G, Thornton EM, Renauld JC *et al*. (2001). Deleterious effects of IL-9-activated mast cells and neuroprotection by antihistamine drugs in the developing mouse brain. Pediatr Res 50: 222–230.

Pillot C, Heron A, Cochois V, Tardivel-Lacombe J, Ligneau X, Schwartz JC *et al*. (2002). A detailed mapping of the histamine H3 receptor and its gene transcripts in rat brain. Neuroscience 114: 173–193.

Pitkanen A (2010). Therapeutic approaches to epileptogenesis – hope on the horizon. Epilepsia 51 (Suppl. 3): 2–17.

Qing H, He G, Ly PT, Fox CJ, Staufenbiel M, Cai F *et al*. (2008). Valproic acid inhibits Abeta production, neuritic plaque formation, and behavioral deficits in Alzheimer's disease mouse models. J Exp Med 205: 2781–2789.

Rakhade SN, Yao B, Ahmed S, Asano E, Beaumont TL, Shah AK *et al*. (2005). A common pattern of persistent gene activation in human neocortical epileptic foci. Ann Neurol 58: 736–747.

Rane MJ, Coxon PY, Powell DW, Webster R, Klein JB, Pierce W *et al*. (2001). p38 kinase-dependent MAPKAPK-2 activation functions as 3-phosphoinositide-dependent kinase-2 for Akt in human neutrophils. J Biol Chem 276: 3517–3523.

Rickle A, Bogdanovic N, Volkman I, Winblad B, Ravid R, Cowburn RF (2004). Akt activity in Alzheimer's disease and other neurodegenerative disorders. Neuroreport 15: 955–959.

Rosa AO, Egea J, Martínez A, García AG, López MG (2008). Neuroprotective effect of the new thiadiazolidinone NP00111 against oxygen-glucose deprivation in rat hippocampal slices: implication of ERK1/2 and PPARγ receptors. Exp Neurol 212: 93–99.

Rouleau A, Ligneaux X, Tardivel-Lacombe J, Morisset S, Gbahou F, Schwartz JC *et al*. (2002). HistamineH3-receptor-mediated [^{35}S]GTPγS binding: evidence for constitutive activity of the recombinant and native rat and human H3 receptors. Br J Pharmacol 135: 383–392.

Rowley NM, Madsen KK, Schousboe A, Steve White H (2012). Glutamate and GABA synthesis, release, transport and metabolism as targets for seizure control. Neurochem Int DOI: 10.1016/j.neuint.2012.02.013 [Epub ahead of print].

Sakamoto K, Karelina K, Obrietan K (2011). CREB: a multifaceted regulator of neuronal plasticity and protection. J Neurochem 116: 1–9.

Scherkl R, Hashem A, Frey HH (1991). Histamine in brain – its role in regulation of seizure susceptibility. Epilepsy Res 10: 111–118.

Schlicker E, Malinowska B, Kathmann M, Göthert M (1994). Modulation of neurotransmitter release via histamine H3 heteroreceptors. Fundam Clin Pharmacol 8: 128–137.

Schwartz JC (2011). The histamine H3 receptor: from drug discovery to clinical trials with pitolisant. Br J Pharmacol 163: 713–721.

Schwartz JC, Arrang JM, Garbarg M, Gulat-Marnay C, Pollard H (1990). Modulation of histamine synthesis and release in brain via presynaptic auto and heteroreceptors. Ann N Y Acad Sci 604: 40–54.

Seyedi N, Mackins CJ, Machida T, Reid AC, Silver RB, Levi R (2005). Histamine H3-receptor-induced attenuation of norepinephrine exocytosis: a decreased protein kinase A activity mediates a reduction in intracellular calcium. J Pharmacol Exp Ther 312: 272–280.

Shen Y, Hu WW, Fan YY, Dai HB, Fu QL, Wei EQ *et al*. (2007). Carnosine protects against NMDA-induced neurotoxicity in differentiated rat PC12 cells through carnosine-histidine-histamine pathway and H(1)/H(3) receptors. Biochem Pharmacol 73: 709–717.

Sherin JE, Elmquist JK, Torrealba F, Saper CB (1998). Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. J Neurosci 18: 4705–4721.

Silver RB, Mackins CJ, Smith NC, Koritchneva IL, Lefkowitz K, Lovenberg TW *et al*. (2001). Coupling of histamine H3 receptors to neuronal Na^+/H^+ exchange: a novel protective mechanism in myocardial ischemia. Proc Natl Acad Sci U S A 98: 2855–2859.

Silver RB, Poonwasi KS, Seyedi N, Wilson SJ, Lovenberg TW, Levi R (2002). Decreased intracellular calcium mediates the histamine H_3-receptor-induced attenuation of norepinephrine exocytosis from cardiac sympathetic nerve endings. Proc Natl Acad Sci U S A 99: 501–506.

Singh D, Goel RK (2010). Proconvulsant potential of cyproheptadine in experimental animal models. Fundam Clin Pharmacol 24: 451–455.

Sloviter RS (2011). Progress on the issue of excitotoxic injury modification vs. real neuroprotection; implications for post-traumatic epilepsy. Neuropharmacology 61: 1048–1050.

Sturman G, Freeman P, Meade HM, Seeley NA (1994). Modulation of the intracellular and H3-histamine receptors and chemically-induced seizures in mice. Agents Actions 41: C68–C69.

Subramaniam S, Unsicker K (2010). ERK and cell death: ERK1/2 in neuronal death. FEBS J 277: 22–29.

Sun GY, Shelat PB, Jensen MB, He Y, Sun AY, Simonyi A (2010). Phospholipases A2 and inflammatory responses in the central nervous system. Neuromolecular Med 12: 133–148.

Takano T, Sakaue Y, Sokoda T, Sawai C, Akabori S, Maruo Y *et al*. (2010). Seizure susceptibility due to antihistamines in febrile seizures. Pediatr Neurol 42: 277–279.

Takashima A (2009). Drug development targeting the glycogen synthase kinase-3β (GSK-3β)- mediated signal transduction pathway: role of GSK-3β in adult brain. J Pharmacol Sci 109: 174–178.

Tashiro M, Yanai K (2007). [Molecular imaging of histamine receptors in the human brain]. [Article in Japanese] Brain Nerve 59: 221–231.

Tiligada E, Zampeli E, Sander K, Stark H (2009). Histamine H3 and H4 receptors as novel drug targets. Expert Opin Investig Drugs 18: 1519–1531.

Torrent A, Moreno-Delgado D, GóMEZ-Ramírez J, Rodríguez-Agudo D, Rodríguez-Caso C, SáNCHEZ-Jiménez F *et al*. (2005). H3 autoreceptors modulate histamine synthesis through calcium/calmodulin- and cAMP-dependent protein kinase pathways. Mol Pharmacol 67: 195–203.

Tuomisto L, Tacke U (1986). Is histamine an anticonvulsive inhibitory transmitter? Neuropharmacology 25: 955–958.

Tuomisto L, Tacke U, Willman A (1987). Inhibition of sound-induced convulsions by metoprine in the audiogenic seizure susceptible rat. Agents Actions 20: 252–254.

Turturici G, Sconzo G, Geraci F (2011). Hsp70 and its molecular role in nervous system diseases. Biochem Res Int 2011: ID-618127.

Uma Devi P, Manocha A, Khanam R, Vohora D (2011). Beneficial interaction between clobenpropit and pyridoxine in prevention of electroshock-induced seizures in mice: lack of histaminergic mechanisms. Hum Exp Toxicol 30: 84–88.

Valor LM, Jancic D, Lujan R, Barco A (2010). Ultrastructural and transcriptional profiling of neuropathological misregulation of CREB function. Cell Death Differ 17: 1636–1644.

Vohora D, Pal SN, Pillai KK (2000). Thioperamide, a selective histamine H_3 receptor antagonist, protects against PTZ-induced seizures in mice. Life Sci 66: PL297–PL301.

Vohora D, Pal SN, Pillai KK (2001). Histamine and selective H_3 receptor ligands: a possible role in the mechanism and management of epilepsy. Pharmacol Biochem Behav 68: 735–741.

Vohora D, Khanam R, Pal SN, Pillai KK (2010). Effect of combined treatment of thioperamide with some antiepileptic drugs on methionine-sulfoximine induced convulsions in mice. Indian J Exp Biol 48: 858–860.

Wada T, Penninger JM (2004). Mitogen-activated protein kinases in apoptosis regulation. Oncogene 23: 2838–2849.

Wada Y, Shiraishi J, Nakamura M, Koshino Y (1996). Biphasic action of the histamine precursor L-histidine in the rat kindling model of epilepsy. Neurosci Lett 204: 205–208.

Walker M (2007). Neuroprotection in epilepsy. Epilepsia 48 (Suppl. 8): 66–68.

Watanabe T, Taguchi Y, Shiosaka S, Tanaka J, Kubota H, Terano Y *et al*. (1984). Distribution of the histaminergic neuron system in the central nervous system of rats: a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res 295: 13–25.

Werner FM, Coveñas R (2011). Classical neurotransmitters and neuropeptides involved in generalized epilepsy: a focus on antiepileptic drugs. Curr Med Chem 18: 4933–4948.

Wieland K, Bongers G, Yamamoto Y, Hashimoto T, Yamatodani A, Menge WM *et al*. (2001). Constitutive activity of histamine H(3) receptors stably expressed in SK-N-MC cells: display of agonism and inverse agonism by H(3) antagonists. J Pharmacol Exp Ther 299: 908–914.

Willmore LJ (2005). Antiepileptic drugs and neuroprotection: current status and future roles. Epilepsy Behav 7: S25–S28.

Wouterlood FG, Sauren YM, Steinbusch HW (1986). Histaminergic neurons in the rat brain: correlative immunocytochemistry, Golgi impregnation, and electron microscopy. J Comp Neurol 252: 227–244.

Yanai K, Tashiro M (2007). The physiological and pathophysiological roles of neuronal histamine: an insight from human positron emission tomography studies. Pharmacol Ther 113: 1–15.

Yawata I, Tanaka K, Nakagawa Y, Watanabe Y, Murashima YL, Nakano K (2004). Role of histaminergic neurons in development of epileptic seizures in EL mice. Brain Res Mol Brain Res 132: 13–17.

Yokoyama H, Onodera K, Maeyama K, Yanai K, Iinuma K, Tuomisto L *et al*. (1992). Histamine levels and clonic convulsions of electrically-induced seizure in mice: the effects of a-fluoromethylhistidine and metoprine. Naunyn Schmiedebergs Arch Pharmacol 346: 40–45.

Yokoyama H, Onodera K, Iinuma K, Watanabe T (1993a). Proconvulsive effects of histamine H1-antagonists on electrically-induced seizure in developing mice. Psychopharmacology (Berl) 112: 199–203.

Yokoyama H, Iinuma K, Yanai K, Watanabe T, Sakurai E, Onodera K (1993b). Proconvulsant effect of ketotifen, a histamine H1 antagonist, confirmed by the use of d-chlorpheniramine with monitoring electroencephalography. Methods Find Exp Clin Pharmacol 15: 183–188.

Yokoyama H, Onodera K, Iinuma K, Watanabe T (1993c). Effect of thioperamide, a histamine H_3 receptor antagonist, on electrically induced convulsions in mice. Eur J Pharmacol 234: 129–133.

Yokoyama H, Onodera K, Maeyama K, Sakurai E, Iinuma K, Leurs R *et al*. (1994). Clobenpropit (VUF-9153), a new histamine H3 receptor antagonist, inhibits electrically induced convulsions in mice. Eur J Pharmacol 260: 23–28.

Yokoyama H, Sato M, Iinuma K, Onodera K, Watanabe T (1996). Centrally acting histamine H1 antagonists promote the development of amygdala kindling in rats. Neurosci Lett 217: 194–196.

Yokoyama H, Onodera K, Yagi T, Iinuma K (1997). Therapeutic doses of theophylline exert proconvulsant effects in developing mice. Brain Dev 19: 403–407.

Yoshida M, Noguchi E, Tsuru N (2000). Lack of substantial effect of the H(3)-antagonist thioperamide and of the non-selective mixed H(3)-antagonist/H(1)-agonist betahistine on amygdaloid kindled seizures. Epilepsy Res 40: 141–145.

Zhang LS, Chen Z, Huang YW, Hu WW, Wei EQ, Yanai K (2003a). Effects of endogenous histamine on seizure development of pentylenetetrazole-induced kindling in rats. Pharmacology 69: 27–32.

Zhang LS, Chen Z, Ren K, Leurs R, Chen J, Zhang W *et al*. (2003b). Effects of clobenpropit on pentylenetetrazole-kindled seizures in rats. Eur J Pharmacol 482: 169–175.

Zhang LS, Shen HQ, Jin CL, Hu WW, Zhao MH, Chen Z (2004). Mechanisms of the effect of brain histamine on chronic epilepsy induced by pentylenetetrazole [Article in Chinese]. Zhejiang Da Xue Xue Bao Yi Xue Ban 33: 201–204.

Zhao P, Ma MC, Qian H, Xia Y (2005). Down-regulation of delta-opioid receptors in Na^+/H^+ exchanger 1 null mutant mouse brain with epilepsy. Neurosci Res 53: 442–446.

Zhu X, Han X, Blendy JA, Porter BE (2012). Decreased CREB levels suppress epilepsy. Neurobiol Dis 45: 253–263.

Zhu YY, Zhu-Ge ZB, Wu DC, Wang S, Liu LY, Ohtsu H *et al*. (2007). Carnosine inhibits pentylenetetrazol-induced seizures by histaminergic mechanisms in histidine decarboxylase knock-out mice. Neurosci Lett 416: 211–216.

Zimatkin SM, Kuznetsova VB, Strik ON (2006). Spatial organization and morphometric characteristics of histaminergic neurons in the rat brain. Neurosci Behav Physiol 36: 467–471.