

REVIEW

Histamine H₃ receptor antagonists in relation to epilepsy and neurodegeneration: a systemic consideration of recent progress and perspectives

M Bhowmik, R Khanam and D Vohora

Neurobehavioral Pharmacology Laboratory, Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi, India

Correspondence

D Vohora, Neurobehavioral Pharmacology Laboratory, Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi 110062, India. E-mail: divyavohora@hotmail.com; dvohra@jamiahamdard.ac.in

Keywords

histamine H₃ receptor antagonists; epilepsy; neurodegeneration and neurotoxicity; H₃ receptor signalling pathways

Received

9 March 2012

Revised

3 May 2012

Accepted

12 June 2012

The central histaminergic actions are mediated by H₁, H₂, H₃ and H₄ receptors. The histamine H₃ 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 H₃ 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, H₃ 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 H₃ receptor antagonists, thus improving their utility in epilepsy and associated neurotoxicity.

Abbreviations

[³⁵S]-GTPγS, [³⁵S]-guanosine 5'-γ-thiotriphosphate; [Ca²⁺]_i, intracellular calcium; 3-NP, 3-nitropropionic acid; AA, arachidonic acid; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; AEDs, antiepileptic drugs; CaMKII, Ca²⁺-activated calmodulin kinases; CREB, cAMP-responsive-element-binding protein; HDC, histidine decarboxylase; hH₃ receptor, human H₃ 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 H₃ 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 H₃ 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 H₁ and H₃ 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 H₃ 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 H₃ 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 H₃ 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 H₃ 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 (H₁₋₄; Parsons and Ganellin, 2006; Nuutinen and Panula, 2010), of which H₁₋₃ receptors are very widely expressed throughout the mammalian brain (Garbarg and Schwartz, 1985; Hill *et al.*, 1997; Tashiro and Yanai, 2007). For the H₃ 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 (H₁ and H₂) are located postsynaptically and are found in the CNS and periphery (reviewed in Parsons and Ganellin, 2006), whereas the recently discovered H₄ 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 H₃ 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 H₃ 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 H₃ receptors (*hH₃* 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 H₃ 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 H₃ 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 H₃ 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 H₃ 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).

H₃ 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 *hH₃* receptor gene pioneered by Tim Lovenberg in 1999, H₃ 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 H₃ receptor was confirmed by the heterologous expression of the H₃ 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 H₃ receptor function (Rouleau *et al.*, 2002) and [³⁵S]-GTPγS binding studies in rat brain (Clark and Hill, 1996).

Studies using recombinant cell systems have revealed that brain H₃ 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 H₃ receptors (Figure 1), including inhibition of AC and activation of MAPK (reviewed by Leurs *et al.*, 2005; Bongers *et al.*, 2007a). H₃ receptor activation of G_{i/o}-proteins might also lead to the activation of PLA₂ 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 Ca²⁺ ([Ca²⁺]_i) levels (Silver *et al.*, 2002). In view of the interest in the H₃ receptor as a potential therapeutic target, each of these signalling path-

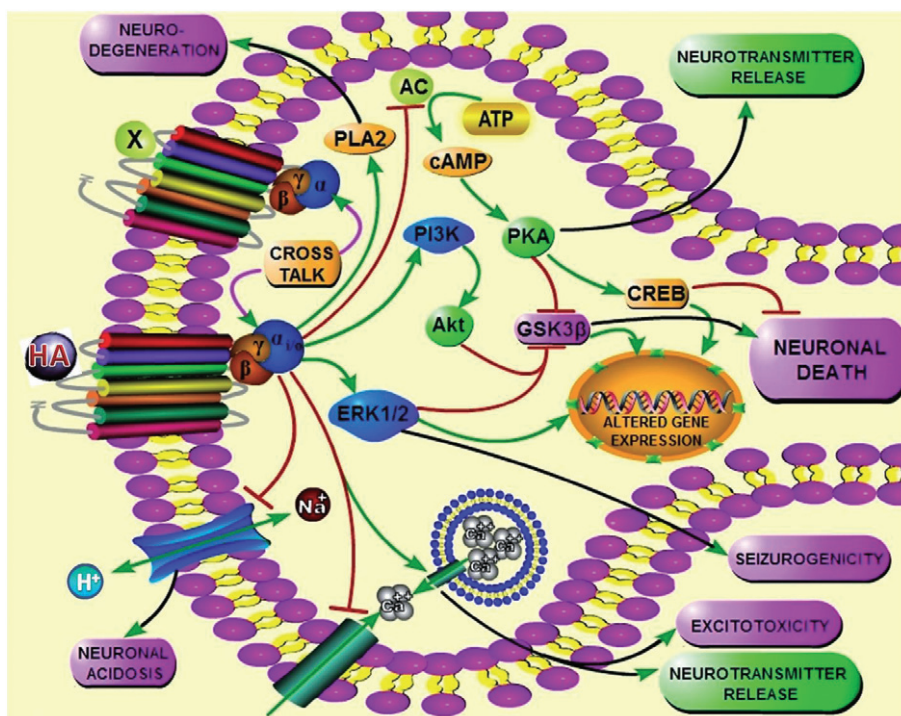


Figure 1

The schematic diagram is a hypothetical depiction of the H₃ receptor-mediated signalling pathways in the CNS and their probable implications. Activation of H₃ 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, H₃ 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 H₃ receptors; activated ERK has also been linked to epilepsy. The other three pathways known so far that are modulated upon H₃ receptor activation include increased activity of the enzyme PLA₂, whose inhibition confers neuroprotection in epileptic models; mobilization of intracellular Ca²⁺ [Ca²⁺]_i; and finally the inhibition of Na⁺/H⁺ exchanger (NHE), a protein that buffers intra-neuronal pH and its defective functioning is also implicated in epilepsy. Also, H₃ receptors possibly influence the function of other GPCRs and *vice versa* (e.g. dopamine D₁ 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 H₃ receptor negatively couples to AC; hence, H₃ 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 H₃ 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 H₃ 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 (H₃ 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), Ca²⁺-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 H₃ 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 H₃ 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 H₃ receptor pathways remains to be further examined, as H₃ 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 H₃ (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 H₃ receptors.

However, in rat hippocampal CA3 pyramidal cells H₃ 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 H₃ receptor signalling pathway in the aetiology of chronic epilepsies has yet to be ascertained.

Activation of the PI3K/Akt/GSK3 β axis

H₃ 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-3 β (pGSK-3 β_{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-3 β 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-3 β axis has emerged as a potential target for various neurological disorders. Activation of GSK-3 β (pGSK-3 β_{lyr216}) promotes apoptosis in a wide variety of conditions, while its inhibition promotes cell survival (Rickle *et al.*, 2004; Takashima, 2009). The role of H₃ receptor-mediated activation of Akt/GSK-3 β in the brain is still under investigation, but dysregulation of GSK-3 β 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-3 β suggests a potential role for its inhibitors in protection against neuronal cell death (Eldar-Finkelman, 2002; Takashima, 2009). Inhibition of GSK-3 β 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-3 β 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-3 β has also been implicated in the mechanism of action of AEDs like valproic acid (Qing *et al.*, 2008), suggesting a possible role for GSK-3 β in the pathophysiology of epilepsy.

The novel finding that stimulation of H₃ receptors triggers activation of the Akt/GSK-3 β pathway and protects against NMDA-induced neurotoxicity, and that both are blocked by the H₃-antagonist thioperamide (Bongers *et al.*, 2007b; Mariottini *et al.*, 2009), is contradicted by an *in vivo* study where inhibition of H₃ receptors by the H₃-antagonist ABT-239 conferred neuroprotection by elevating hippocampal GSK-3 β_{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 H₃ 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 H₃ receptors are coupled to GSK-3 β throws up an exciting

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

Activation of PLA₂

H₃ receptor-induced activation of G_{i/o}-proteins seems to stimulate PLA₂ to induce the release of AA (Rouleau *et al.*, 2002). Usually, activation of mammalian PLA₂ 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 PLA₂ 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 H₃ receptor ligands.

Inhibition of the Na⁺/H⁺ exchanger

H₃ 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_{α_{i/o}}-proteins has been proposed (Bongers *et al.*, 2007a). Activation of the H₃ receptor was shown to diminish neuronal NHE activity, and this pathway is proposed as the mechanism by which the H₃ 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 H₃ receptor ligands on NHE and subsequent implications in epilepsy need to be assessed.

Modulation of [Ca²⁺]_i

Neuronal H₃ 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, H₃ receptor agonists, acting on recombinantly expressed H₃ receptors, transiently mobilize calcium from intracellular depots (Bongers *et al.*, 2006). To complicate this further, the H₃ receptor antagonist clobenpropit was found to reverse NMDA-induced Ca²⁺ 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 H₃ 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 Ca²⁺ homeostasis and Ca²⁺ signalling via CaMKII regulate neuronal well-being. Ca²⁺ 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 H₃ receptor-mediated alteration in neuronal [Ca²⁺]_i level pertaining to epileptogenesis still need to be elucidated.

Epilepsy and histamine H₃ 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 H₁ 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 H₁ 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 H₃ receptors in epilepsy is currently under investigation. The pharmacological properties of H₃ 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

H₃ receptor antagonists. They were found to protect against experimental convulsions by increasing the release of histamine in the brain, which in turn interacts with H₁ receptors (Yokoyama *et al.*, 1993; 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 H₃ 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 photoparoxysmal response. The onset of action was 1–2 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 H₃ 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 H₁- and H₃-dependent mechanism. In line with this, H₃ 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 H₃ 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 H₁ and H₃ receptors (Kukko-Lukjanov *et al.*, 2006; 2012). Likewise, KA-induced neurotoxicity was aggravated in mice treated with an H₁-receptor antagonist (Kukko-Lukjanov *et al.*, 2010). At present, there is very little information regarding the effect of H₃ antagonists on neuronal survival and function. A role for histamine H₃ 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 H₂ receptor (Dai *et al.*, 2006).

Unlike the anticonvulsive role attributed to H₃ receptors in several studies, relatively little attention has been paid to their possible neuroprotective role especially in seizure-associated neurotoxicity. H₃ receptor-dependent modulation of neuroprotective mechanisms has also been demonstrated in diverse studies. A robust up-regulation of H₃ receptor mRNA was observed in certain brain areas that participate in epileptogenic processes after KA-induced seizures, indicative of a modulatory role of H₃ receptors (Lintunen *et al.*, 2005) as well as during experimental ischaemia (Lozada *et al.*, 2005). Increased H₃ receptor expression and subsequent constitutive activation of the downstream Akt/GSK-3 β pathway could be the mechanism by which the H₃ receptor exerts its endogenous neuroprotective role (Bongers *et al.*, 2007b). On the flip side and in line with an antiepileptic mechanism, H₃ receptor agonism aggravated delayed neuronal death in a rat model of cerebral ischaemia (Adachi *et al.*, 1993). Moreover, H₃ receptor antagonism conferred neuroprotection by elevating the hippocampal GSK-3 β _{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 H₃ receptor antagonist was found to provide neuroprotection arising from their interaction with HSPs in a KA-induced neurotoxic model in teleost (Giusti *et al.*, 2008).

The role of H₃ receptor ligands in neuroprotection is further confounded by a number of discrepancies that have emerged (Table 2). H₃ 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 H₃ 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 H₃ receptor isoforms (particularly H_{3A+B}) 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 1H₃ receptor ligands and the mechanisms entailed in their antiepileptic effect in diverse models of epilepsy

H ₃ receptor ligands	Model used	Effect observed	Mechanism	Reference
Thiopropamide (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 <i>et al.</i> , 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 <i>et al.</i> , 1994
AQ-0145	MES seizure in mice	↓ Duration of each phase of convulsion	As first mechanism	Murakami <i>et al.</i> , 1995
Thiopropamide (7.5 and 15 mg·kg ⁻¹ i.p.)	Proconvulsive effect of theophylline on MES seizure in mice	↓ Mortality	As first mechanism	Yokoyama <i>et al.</i> , 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
Thiopropamide (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 <i>et al.</i> , 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 <i>et al.</i> , 2000
Thiopropamide (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 <i>et al.</i> , 2000
Thiopropamide 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
Thiopropamide (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 <i>et al.</i> , 2001
Thiopropamide (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 <i>et al.</i> , 2002
Clobenpropit (10 and 20 µg i.c.v.) Imnepip (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 <i>et al.</i> , 2003a,b
Carcinine and Thiopropamide (each 2–20 mg·kg ⁻¹ i.p.)	PTZ induced kindling in mice	↑ Latency of seizures; ↓ Seizure stages	↑ HDC activity; ↑ HA release	Chen <i>et al.</i> , 2004
Iodophenpropit, Clobenpropit, Thiopropamide (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 <i>et al.</i> , 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 <i>et al.</i> , 2004
Clobenpropit (i.c.v.)	PTZ-induced kindling in mice	↑ Latency of myoclonic jerks and clonic generalized seizures; ↓ Seizure stages	As first mechanism	Zhang <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2011
Thioperamide (2–10 mg·kg ⁻¹ i.p.) and <i>R</i> -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 <i>et al.</i> , 1991
Thioperamide and Burimamide	Picrotoxin induced seizure	↑ Severity of clonic convulsions	H ₃ antagonism	Sturman <i>et al.</i> , 1994
Thioperamide (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 <i>et al.</i> , 2000
Thioperamide (15 mg·kg ⁻¹ i.p.)	Methionine-sulfoximine induced convulsion in mice	⊗ Seizure latency and mortality	H ₃ antagonism	Vohora <i>et al.</i> , 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 H₃ receptors, which was comparable with deleterious neuronal effects in rat and hamster (Canonaco *et al.*, 2005). In summary, H₃ 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 H₃ 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 anti-

convulsive and neuroprotective effects of H₃ 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 H₃ receptors in the inhibition of seizures, the development of *h*H₃ 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 H₃ 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, H₃ 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

H₃ 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 <i>et al.</i> , 2001
Thioperamide (10 ⁻⁸ –10 ⁻⁵ M)	HA-induced neurotoxicity in cultured rat cerebellar granular neurons	↓ % of cell death	As 1 st mechanism	Gepdiremen <i>et al.</i> , 2003
Thioperamide (10 mg·kg ⁻¹ i.p.)	3-NP-induced neurotoxicity in hamster	↑ H ₁ R mRNA, ↓ Motor behaviour	As 1 st mechanism	Canonaco <i>et al.</i> , 2005
Thioperamide (10 ⁻⁷ –10 ⁻⁵ M)	NMDA-induced neurotoxicity in cultured rat cortical neurons	↓ NMDA-induced necrosis, ↑ Neuronal viability	As 1 st mechanism, ↑ GABA release	Dai <i>et al.</i> , 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 1 st mechanism	Kukko-Lukjanov <i>et al.</i> , 2006
Clobenpropit (10 ⁻¹¹ –10 ⁻⁷ M)	NMDA-induced neurotoxicity in cultured rat cortical neurons	↓ NMDA-induced necrosis, ↑ Neuronal viability	As 1 st mechanism; Activation of cAMP/PKA pathway; ↑ GABA release, ↓ [Ca ²⁺] _i	Dai <i>et al.</i> , 2007
Thioperamide (10 mg·kg ⁻¹ i.p.)	Pb-induced neurotoxicity in teleost (<i>T. pavo</i>)	↓ Behavioural hyperactivity, ↓ Neurodegeneration, ↓ mRNA expression of HSPs (70 and 90)	Cross-talk between H ₃ R with HSPs	Giusi <i>et al.</i> , 2008
GSK 189254 (0.3 mg·kg ⁻¹ p.o.)	GSK 189254-treated rats	↑ Survival of dentate gyrus neurons	↑ NCAM-PSA expression	Foley <i>et al.</i> , 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 1 st mechanism	Bitner <i>et al.</i> , 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 1 st mechanism	Shen <i>et al.</i> , 2007
Thioperamide (10 μM·L ⁻¹) Clobenpropit (100 μM·L ⁻¹)	SK-N-MC cells transfected with hH ₃ R; Cultured rat cortical neurons and striatal slices	↑ cAMP accumulation, ↓ pAkt _{ser473} , ↓ p-GSK3β _{ser9}	As 1 st mechanism	Bongers <i>et al.</i> , 2007b
Thioperamide (1 μM)	Cultured rat cortical stem cells	⊗ Cell proliferation and differentiation	As 1 st 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 1 st mechanism	Fu <i>et al.</i> , 2008
Thioperamide (10 μM·L ⁻¹) Immeipip (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; ⊗ <i>per se</i> on the above	As 1 st mechanism	Mariottini <i>et al.</i> , 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 <i>et al.</i> , 2005
–	KA in SD rats	Variable (site & time dependent)- Both anti- and/or seizurogenic; from neuronal death to survival/regeneration	Transient expression of- ↑↑ H _{3A+D} mRNA followed by ↓ H _{3A+D} mRNA	Lintunen <i>et al.</i> , 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 H₃R; SD, Sprague–Dawley; ↑ increase; ↑↑ very high increase; ↓ decrease; – no H₃R ligand used; ⊗ no change.

expression of H₃ 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 H₃ 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 H₃ 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 H₃ 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 H₃ receptor agonism *in vitro* (Bongers *et al.*, 2007b) leads to signalling changes in the Akt/GSK-3 β pathway analogous to those observed with H₃ 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 H₃ receptor is essential in order to elucidate the molecular mechanisms underlying the potential H₃ 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 H₃ agonism and antagonism have been found to attenuate Ca²⁺ influx and [Ca²⁺]_i levels. The possible explanation for these inconsistencies in H₃ receptor-mediated Ca²⁺ 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 H₃ 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 H₃ 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 H₃ receptors as demonstrated by the transient and variable expression of various H₃ 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, H₃ 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 H₃ 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 H₃ 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 H₃ 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 H₃ 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 H₃ receptor. *Biochem Pharmacol* 73: 1195–1204.
- Bongers G, Sallmen T, Passani MB, Mariottini C, Wendelin D, Lozada A *et al.* (2007b). The Akt/GSK-3 β 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, Rizzo 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 pentylentetrazole-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 pentylentetrazole 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 carbinine on histaminergic neurons in the brain. *Br J Pharmacol* 143: 573–580.
- Chin PC, Majdzadeh N, D'Mello SR (2005). Inhibition of GSK-3 β 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 [³⁵S]GTP γ S 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 H₃ 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 H₃ 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 Aβ₄₂-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 H₃ 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-3β 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 epilepsy. *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 receptors in 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 H₁ 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 H₃ 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 H₃ receptor ligands making the final push towards the market? *Expert Opin Investig Drugs* 20: 1629–1648.
- Kukko-Lukjanov TK, Soim 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, Obrietan 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 H₃ 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). Postschismic 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 H₃ 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-García AA, Medina MA, Sánchez-Jiménez 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, Renaud 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, Ligneaux 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, Staufienbiel 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 PPAR γ 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]GTP γ S 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 H₃-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-3 β (GSK-3 β)-mediated signal transduction pathway: role of GSK-3 β 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 H₃ receptor antagonist, protects against PTZ-induced seizures in mice. *Life Sci* 66: PL297–PL301.
- Vohora D, Pal SN, Pillai KK (2001). Histamine and selective H₃ 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 H₃ receptors stably expressed in SK-N-MC cells: display of agonism and inverse agonism by H₃ 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 α -fluoromethylhistidine and metoprine. *Naunyn Schmiedeberg 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 H₃ 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 betahistidine 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.