Central Histaminergic Signaling, Neural Excitability and Epilepsy

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Abstract

Epilepsy is a common neurological disorder characterized by repeated and spontaneous epileptic seizures, which is not well controlled by current medication. Traditional theory supports that epilepsy results from the imbalance of excitatory glutamate neurons and inhibitory GABAergic neurons. Recently, shreds of evidence from available clinical and preclinical researches suggest that histamine in the central nervous system plays an important role in the modulation of neural excitability and pathogenesis of epilepsy. Many histamine receptor ligands show positive response in animal epilepsy models, among which the H3R antagonist pitolisant even has shown a good anti-epileptic effect in clinical trials. New insights are focusing on the potential action of histamine receptors to control and treat epilepsy. This review summarizes the findings from animal and clinical researches on the role of brain histamine and histamine receptor in epilepsy. Importantly, we further provide perspectives on some possible research directions for future studies.

Central Histaminergic Signaling, Neural Excitability and Epilepsy

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Abstract

Epilepsy is a common neurological disorder characterized by repeated and spontaneous epileptic seizures, which is not well controlled by current medication. Traditional theory supports that epilepsy results from the imbalance of excitatory glutamate neurons and inhibitory GABAergic neurons. Recently, shreds of evidence from available clinical and preclinical researches suggest that histamine in the central nervous system plays an important role in the modulation of neural excitability and pathogenesis of epilepsy. Many histamine receptor

ligands show positive response in animal epilepsy models, among which the H3R antagonist pitolisant even has shown a good anti-epileptic effect in clinical trials. New insights are focusing on the potential action of histamine receptors to control and treat epilepsy. This review summarizes the findings from animal and clinical researches on the role of brain histamine and histamine receptor in epilepsy. Importantly, we further provide perspectives on some possible research directions for future studies.

Keywords: epilepsy, histamine, histamine receptor, central nervous system

Abbreviations

AA, arachidonic acid; ADD, afterdischarge duration; AC, adenylate cyclase; AEDs, anti-epileptic drugs; AGS, audiogenic seizure; ASP, Anticonvulsant Screening Program; cGMP, cyclic guanosine monophosphate; CNS, central nervous system; CREB, cAMP response element-binding; DAG, diacylglycerol; DBS: deep brain stimulation; DRE, drug-resistant epilepsy; EL, epilepsy like; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase 3β· HCN, hyperpolarization-activated cyclic nucleotide-gated; HDC, histidine-decarboxylase; HFS, high-frequency stimulation; HNMT, histamine N-methyltransferase; H1R, histamine H1 receptor; H2R, histamine H2 receptor; H3R, histamine H3 receptor; H4R, histamine H4 receptor; IP_3, phosphatidyl inositol-4, 5-biphosphate; KA, Kainic acid; KM, Krushinski-Molodkina; KO, knock out; LFS, low-frequency stimulation; MAPK, mitogen-activated protein kinase; MES, maximal electroshock seizure; MTLE, mesial temporal lobe epilepsy; NINDS/NIH, National Institute of Neurological Disorders and Stroke/National Institutes of Health; PLA2, phospholipase A2; PKA, phosphokinase A; PKC, phosphokinase C; PTZ, pentylenetetrazole; RGC, retrosplenial granular cortex; STR, strychnine; TMN, tuberomammillary nucleus; VMAT-2, Vesicular monoamine transporter-2; WT, wide type

1. Introduction

Epilepsy is one kind of common neurologic disease, affecting up to 70 million people worldwide (Trinka, Kwan, Lee & Dash, 2019). Anti-epileptic drugs (AEDs) are the first choice for most patients. Even so, the adverse effects of AEDs lead to improper seizure control of many patients. What's worse, there is approximately one-third of patients become drug-resistant epilepsy (DRE) (Löscher, Klitgaard, Twyman & Schmidt, 2013). For DRE, surgery is the ultimate therapy but less than 1% of patients preferred (Engel, 2018). Alternative treatments, such as deep brain stimulation (DBS), laser interstitial thermal therapy, vagus nerve stimulation and dietary modification, are also used for epilepsy treatment (Kaeberle, 2018; Schaper et al., 2020), but anti-epileptic effects are limited. Above therapeutic challenge in clinical may be due to the fact that the mechanism of epilepsy is not fully understood. Traditional theory supports that epilepsy results from the imbalance of neural excitability. Classically, researches mainly focus on the excitatory glutamatergic neurotransmission and inhibitory GABAergic neurotransmission, both of which are the designed target of most of AEDs.

Pieces of evidence have indicated that other neurontransmitters, including histamine, 5-HT, and acetylcholine, also participating in the modulation of neural excitability and the ictogenesis and epileptogenesis (Meller, Brandt, Theilmann, Klein & Löscher, 2019; Sugitate, Okubo, Nariai & Matsui, 2020; Zhao, Lin, Chen, Li & Huo, 2018). Among them, histamine has been the least understood. Histamine was firstly isolated from the brain cortex by Kwiatkowski in 1943 (Kwiatkowski, 1943). Since then several studies have demonstrated that histamine acts as a neurotransmitter in the brain (Haas, Sergeeva & Selbach, 2008). A decline of histamine content has been found in temporal neocortex of patients with pharmacoresistant mesial temporal lobe epilepsy (MTLE) (Bañuelos-Cabrera et al., 2016). Indeed, several H3R ligands have been discovered to target the epileptic treatment (Sadek, Saad, Sadeq, Jalal & Stark, 2016). This review summarizes the role of histamine and its receptors in neural excitability and epilepsy, and further provides perspectives on future research directions.

2. Histamine and neural excitability

2.1 Histamine and histamine receptors in the brain

The histaminergic neuron is the main source of histamine production in the brain, whose soma is located

in the tuberomammillary nucleus (TMN) of the hypothalamus. The histaminergic neuron fibers are widely distributed in the brain. Neuronal histamine is stored in cell somata and especially in axon varicosities (Haas, Sergeeva & Selbach, 2008). Besides neurons, one study found that cultured microglia also could synthesize histamine (Katoh et al., 2001), while the production of histamine in cerebrovascular endothelial cells is still controversial (Karlstedt et al., 1999; Yamakami et al., 2000). In the peripheral connective tissue, histamine is synthesized and released from mast cells and basophils, which is closely associated with immune response. Stomach enterochromaffin-like cells also give rise to the release of histamine to regulate gastric acid secretion. Interestingly, under some pathological conditions, mast cells can enter the brain. Distinct sources of histamine are shown in Fig.1.

The dietary amino acid L-histidine taken up into neurons by L-amino acid transporter was catalyzed by histidine-decarboxylase (HDC) into histamine by decarboxylation. Neuronal histamine was packaged into vesicles through vesicular monoamine transporter-2 (VMAT-2), and calcium release evokes histamine release from vesicles upon the histaminergic neuron depolarization (Erickson, Schafer, Bonner, Eiden & Weihe, 1996). Then neuronal histamine release into the postsynaptic cleft, which is metabolized into tele-methyhistamine by histamine N -methyltransferase (HNMT) and then degraded into N^l -methylimidazole acetic acid by monoamine oxidase B (Fig.1). Brain histamine modulates several physiological and pathological processes, including sleep-wake cycle, water and food intake, locomotion, neuroendocrine regulation, attention, learning and memory, epilepsy and so on (Sadek, Saad, Sadeq, Jalal & Stark, 2016).There are four histamine receptors have been identified in the brain: histamine H1, H2, H3, and H4 receptors (H1R, H2R, H3R, and H4R). H1R and H2R were postsynaptically located, H3R was both presynaptically and postsynaptically located. It is still controversial that whether H4R is expressed in neurons.

2.2 H1R and neural excitability

The human H1R gene is located on chromosome 3, which encodes a member of the 7-transmembrane, G-protein-associated receptor family (486-491 amino-acids). H1R is coupled with Gq/11 protein and phospholipase C, which in turn hydrolyses phosphatidyl-4, 5-biphosphate to form second messenger, diacylglycerol (DAG) and phosphatidyl inositol-4, 5-biphosphate ($IP_{3)}$ (Leurs, Traiffort, Arrang, Tardivel-Lacombe, Ruat & Schwartz, 1994). DAG activates phosphokinase C (PKC), which in turn induces mitogen-activated protein kinase (MAPK) activation, which involves in neuron synaptic plasticity (Yamamoto et al., 2012). The DAG and IP_3 promote calcium release from the endoplasmic reticulum into the cytoplasm. In addition, H1R activation subsequently leads to formation of arachidonic acid (AA) and cyclic guanosine monophosphate (cGMP). The H1R is widely distributed in the brain, including thalamus, cortex, basal forebrain, raphe nuclei, hypothalamus, septal nuclei, amygdala, hippocampus, locus corelus, nucleus accumbens, and nucleus tractus solitaries as well as cerebellum. The central H1R is mainly corresponding for the side effects of antihistamine drugs.

Most of H1R mediates either excitatory or inhibitory response of histamine in neurons, depending on different brain regions. For example, through H1R, histamine elicits neuronal excitability in the ventromedial hypothalamus and GABAergic neurons in both substantia nigra and ventral tegmental area, and the K^+ channel is involved in that (Korotkova, Haas & Brown, 2002; Zhou, Lee, Devidze, Zhang, Kow & Pfaff, 2007). However, H1R also negatively regulate the neuronal excitability. For instance, H1R decreases cell excitability of hippocampal pyramidal neurons through activation of K^+channels by increase of Ca^{2+} (Selbach, Brown & Haas, 1997). Similarly, H1R antagonist led to membrane potential depolarization in superior cervical ganglion neurons via inhibiting KCNQ/M K^+ channel (Liu, Zhang, Wang, Zhang & Zhang, 2008).

2.3 H2R and neural excitability

The human H2R gene is located on chromosome 5, encoding 7-transmembrane G-protein coupled receptor (359 amino-acids) (Traiffort, Vizuete, Tardivel-Lacombe, Souil, Schwartz & Ruat, 1995). The H2R is coupled to Gs G-protein, which in turn activates adenylyl cyclase to form a second messenger cAMP. Then cAMP activates phosphokinase A (PKA), which in turn phosphorylates downstream targets, such as cAMP response element-binding (CREB) protein. Similar to H1R, the distribution of H2R in the brain is wide,

including cortex, basal ganglia, hippocampus, amygdala, thalamus, and hypothalamus. The H1R and H2R are colocalized in hippocampus, locus coeruleus, raphe nuclei, substantia nigra and ventral tegmental area.

H2R mainly mediates the neuronal excitability elicited by histamine. Histamine induced excitatory response in globus pallidus neurons and cerebellar dentate nucleus neurons, as well as cerebellar Purkinje cells through H2 receptors (Chen, Wang, Yung, Chan & Chow, 2005; Qin et al., 2011; Tian, Wen, Li, Zuo & Wang, 2000), which linked to intracellular G-protein-adenylate cyclase (AC)- PKA signaling pathway (Chen, Wang, Yung, Chan & Chow, 2005). Additionally, histamine elicits excitatory response in the lateral vestibular nucleus neurons in rats, which is co-mediated by the H2R linked-hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and K^+ channels (Li et al., 2016).

Many studies have confirmed that activation of both postsynaptic H1R and H2R co-mediates histamine induced-neuron excitability in several kinds of neurons. For instance, histamine excites dopamine D1 and D2 receptor-expressing striatal GABAergic medium spiny projection neurons, nucleus basalis cholinergic neurons, substantia nigra pars reticulate inhibitory projection neurons, GABAergic ventral pallidum neurons, superior vestibular nuclear neurons, and inferior vestibular nucleus neurons via postsynaptic H1R and H2R (Ji et al., 2018; Khateb, Fort, Pegna, Jones & Mühlethaler, 1995; Peng, Zhuang, He, Zhu & Wang, 2013; Zhou, Xu, Zhao, LeDoux & Zhou, 2006; Zhuang, Wu, Wu, Zhu & Wang, 2013; Zhuang et al., 2018). In medial vestibular nuclear neurons, histamine induces strong postsynaptic excitatory action by Na+-Ca^{2}+ exchangers coupled to H1R and HCN linked to H2R (Zhang, Yu, Zhuang, Peng, Zhu & Wang, 2013). Additionally, histamine facilitates GABAergic transmission in the rat entorhinal cortex through H1R and H2R by activating Na^+ permeable cation channels and inhibiting inward rectifier K^+ channels (Cilz & Lei, 2017).

2.4 H3R and neural excitability

The human H3R gene is located on chromosome 20, encoding $G_{i/o}$-protein coupled receptor (326-445 amino-acids) (Arrang, Garbarg & Schwartz, 1983). The distribution of H3R has been found in cerebral cortex, nucleus accumbens, striatum, olfactory tubercles and substantia nigra, hippocampus, and hypothalamus. The H3R is located on the soma, axon, dendrites, and varicosities of histaminergic neurons, as well as the axon of non-histaminergic neurons (Stevens, Eriksson, Brown & Haas, 2001). Additionally, it has been found that H3R is located on endothelial cells. The H3R mainly located presynaptically is identified as the autoreceptor to regulate the synthesis and release of histamine in histaminergic neurons and acts as heteroreceptor to regulate other neurotransmitters in non-histaminergic neurons. H3R activation inhibits the calcium channels (Lundius, Sanchez-Alavez, Ghochani, Klaus & Tabarean, 2010), and activates the inwardly-rectifying potassium channels blocking nerve depolarization (De Luca et al., 2016), which inhibits the synthesis and release of histamine and other neurotransmitters, including glutamate, GABA, noradrenaline, dopamine, acetylcholine, and serotonin. The H3R also inhibits AA to form cAMP (Lovenberg et al., 1999), activates MAPK, Akt/glycogen synthase kinase 3β (GSK3β) and phospholipase A2 (PLA2) (Giovannini et al., 2003; Sadek, Saad, Sadeq, Jalal & Stark, 2016). Apart from presynaptic location, it has been reported H3R also present on postsynaptic location in basal ganglia colocalized with dopamine receptor 1 and 2 (Ellenbroek & Ghiabi, 2014).

H3R plays a complex role in the modulation of neural excitability, depending on the targeted neurotransmitter. Histamine inhibits spontaneous GABA release from presynaptic nerve terminals projecting to ventromedial hypothalamic neurons by inhibiting presynaptic P/Q-type Ca^{2+} channels via a G-protein coupled to H3R and this may modulate the excitability of ventromedial hypothalamic neurons (Jang, Rhee, Watanabe, Akaike & Akaike, 2001). H3R reduces the coupling of fast excitatory postsynaptic field potentials to population spikes of hippocampal dentate gyrus granule cells (Varaschin, Rosenberg, Hamilton & Savage, 2014), and inhibits the TMN histaminergic neurons and substantia nigra pars reticulate inhibitory neuron (De Luca et al., 2016; Zhou, Xu, Zhao, LeDoux & Zhou, 2006). It needs to be noted that histamine reduces the excitatory gain of D1-expressing medium spiny neurons in nucleus accumbens core by H3R dependent long-term depression through $G_{\beta\gamma}$-Akt/GSK3β signaling pathway (Manz, Becker, Grueter & Grueter, 2020).

Since H3R discovery, there are kinds of research focus on the drug discovery of these ligands (Szczepanska, Kuder & Kiec-Kononowicz, 2018). Agonists or antagonists target H1R/H2R/H3R or H1R/H2R/H3R knock out (KO) mice are commonly used to study the function of these receptors in the brain (Schneider, Neumann & Seifert, 2014; Toyota et al., 2002).

2.5 H4R and neural excitability

The H4R is recently discovered in the last decades, which is mainly located in microglia in the central nervous system (CNS) (Connelly et al., 2009; Raible, Lenahan, Fayvilevich, Kosinski & Schulman, 1994). At present, it is controversial whether the expression of H4R is on neurons or not (Connelly et al., 2009; Schneider & Seifert, 2016). The human H4R gene is located on chromosome 18, similar to H3R, which is coupled to $G_{i/o}$-protein coupled receptor (Cogé, Guénin, Rique, Boutin & Galizzi, 2001). In the brain, H4R was distributed in the dorsal root ganglia, hippocampus, and cerebral cortex (Yuan & Silberstein, 2018). Similar to other histamine receptors, H4R increases calcium release (Li, Carozza, Shatos, Hodges & Dartt, 2012), which is crucial for regulating neuron synaptic excitability (Carrasco, Jaimovich, Kemmerling & Hidalgo, 2004).

Activation of H4R leads to inhibition of CREB in the cerebellar vermis and prefrontal cortex (Fernandes & Serafim, 2019). Also, H4R targets and inactivates the downstream extracellular signal-regulated kinase (ERK)-CREB pathway (Sanna, Mello, Masini & Galeotti, 2018). H4R antagonists inhibit vestibular neuron activity (Desmadryl et al., 2012), suggests H4R involves in vestibular neuron excitability. Agonists or antagonists target H4R are commonly used to assess the function of H4R in some behavioral and disease phenotypes (Fernandes & Serafim, 2019; Fernandes, Serafim, Gianlorenco & Mattioli, 2017; Sanna, Borgonetti, Masini & Galeotti, 2020; Zhou et al., 2019). Recently years, H4R KO mice were also applied to investigate the behavioral phenotype and its neural function (Sanna, Ghelardini, Thurmond, Masini & Galeotti, 2017).

3. Histamine and its receptors in clinical research for epilepsy

As we mainly mentioned the histamine and its receptors in regulating the neuronal excitability, it is not surprise that histamine would play a role in epilepsy that mainly due to the imbalance of "excitation-inhibition". Next, we address the action of histamine and its receptors in epilepsy in clinical studies and the effect of related ligands targeting the histamine receptor on epilepsy in preclinical trials that are summarized in Table 1.

In 1993, Yokoyama reported a 5-years-old boy increased the number of epileptic discharges after administration of d-chlorpheniramine (H1R antagonist) (Yokoyama, Iinuma, Yanai, Watanabe, Sakurai & Onodera, 1993). Since then, similar evidence has been observed in two 4 and 5 months old infancy, who developed tonic spasm after taking H1R antagonist ketotifen (Yasuhara, Ochi, Harada & Kobayashi, 1998). In children, case report indicated that uptake H1R antagonist desloratadine to treat atopic dermatitis, who develop absence seizure with typical electroencephalogram pathological pattern or idiopathic generalized epilepsy later (Cerminara, El-Malhany, Roberto, Lo Castro & Curatolo, 2013). More seriously, overdose taking the H1R antagonist diphenhydramine or ketotifen developed generalized tonic-clonic seizures and dysrhythmias in a teenager, or even toxic encephalopathy followed by localization-related epilepsy and mild mental retardation in infancy (Labarinas, Meulmester, Greene, Thomas, Virk & Erkonen, 2018; Yokoyama, Hirose, Uematsu, Haginoya, Iinuma & Kimura, 2012). The above findings demonstrated that the H1R antagonist has a pro-seizure effect, especially in case of overtaking.

Except for the action of H1R antagonist, the patient after uptake H2R antagonist also affects epilepsy. For example, a patient treated with famotidine (H2R antagonist) for gastric pain, then presented manic symptoms and developed two generalized seizures after the famotidine was discontinued (von Einsiedel, Roesch-Ely, Diebold, Sartor, Mundt & Bergemann, 2002). However, a larger observational cohort study showed that the use of H2R antagonist was not associated with an increased risk of seizures in the overall population or the cohorts stratified by epilepsy status, which including 8605 patients with seizure compared with 40000 controls (Sáez, González-Pérez, Gaist, Johansson, Nagy & García Rodríguez, 2016). It seems that H2R antagonist might not affect the risk of seizure. However, these findings are not direct evidence that could confirm that the effect of central H1R or H2R on epilepsy.

Autopsy reports could provide more direct evidence for the role of histamine and its receptor in epilepsy. However, related studies are limited. At present, there is only one literature reported that patients with MTLE showed a reduction in the H3R function in the hippocampus, and high efficacy of H3Rs Gai/o protein activation with low tissue contents of histamine in temporal cortex, which suggests the potential protective role of H3R and histamine in MTLE (Bañuelos-Cabrera et al., 2016). Most studies focus on identifying the role of H1R or H2R antagonist in epilepsy. More direct evidence from clinical studies is needed.

Based on the specific high constitutive activity of H3R, the H3R antagonists receive a lot of attention. Many H3R antagonist ligands show a good protective effect on epilepsy in preclinical studies, which we will discuss later. Antagonists of H3R are classified into imidazole-based and non-imidazole-based antagonists. The latter has high selectivity and affinity. The H3R antagonist, pitolisant shows good anti-epileptic effects in clinical. One third of patients received the positive response in phase II and pitolisant suppressed the generalized photoparoxysmal response of all epilepsy patients in the photosensitivity proof of concept model in early phase II clinical trials (Collart Dutilleul et al., 2016; Kasteleijn-Nolst Trenité, Parain, Genton, Masnou, Schwartz & Hirsch, 2013). Currently, pitolisant (WakixR) was approved by the European Commission for the treatment of narcolepsy in March 2016. There are several other H3R antagonists ligands under clinical development for other target indications but not epilepsy (Harwell & Fasinu, 2020). At present, most available clinical researches mainly focus on the effect of histamine receptor-related ligands, especially H1R, H2R, and H3R. Little is known about that the role of H4R in epilepsy from clinical studies. However, how the histamine content change in the subdivide brain, or the distribution change of histamine receptor subtypes, needs to validate further.

4. Histamine and its receptors in animal studies for epilepsy

There are many limitations to clinical researches. Animal models of epileptic seizures have an indispensable role in the advancement of investigating the causal role of histamine and its receptor in epilepsy, have been instrumental in the preclinical development of new antiepileptic agents. The models of epilepsy or seizures can be classified into genetic animal models and acquired animal models. For the former, it includes transgenic mice with spontaneous recurrent seizures, and animals with reflex seizure, such as DBA/2 mice, GEPR, and Krushinski-Molodkina (KM) animals. For the latter, there are usually two common ways to induce seizures in normal animals: electrical induction and chemical induction. Pentylenetetrazole (PTZ), pilocarpine (Ach M receptor agonist), strychnine (STR), kainic acid (KA, glutamate receptors agonists), and picrotoxin ($GABA_A$ receptor antagonist) are commonly used chemical substance to induce seizure. Maximal electroshock seizure (MES), amygdaloid kindling, 6-Hz stimulation and transauricular kindling are commonly used as electrical induction method of seizure. Besides, except for the electrical and chemical indication of seizures in normal animals, there are other seizure-induced models, such as audiogenic stimulation, vestibular stimulation and hyperthermia-induced febrile seizure (Löscher, 2011; Potschka, 2012). Actually, the electrical and chemical induction methods are combined use together in some cases. Next, we summarize findings of changes in histamine level or histamine receptor expression in across chemically and electrically-induced epilepsy animal models, as well as other animal models (Table 2). Moreover, we also pay attention to review the therapeutic effect of histamine or histamine receptors related ligands on epilepsy (Table 3), and genetic interventions, especially genetic-edited animal, as well as other interventions in epilepsy in animal researches. The change of histamine and histamine receptor and the therapeutics effect of histamine related ligands in epilepsy are showed in Fig.2.

4.1 The change of central histaminergic signaling in epilepsy animal models

In the PTZ-induced generalized myoclonic seizures, most studies found that PTZ induced seizure accompanied by a decrease of histamine in the hippocampus, thalamus, and hypothalamus (Alachkar et al., 2020; Chen, Ren, Zhang & Hu, 2012; Singh, Pillai & Mehndiratta, 2014; Zhang, Chen, Chen, He & Hu, 2017; Zhang, Ma & Li, 2006), while no change of histamine in hippocampus and striatum also has been found (Szyndler et al., 2006). A similar phenomenon has been observed in MES-induced generalized tonic-clonic seizures: histamine decreased in the cortex, hippocampus, brainstem and hypothalamus, without changing glutamate and GABA levels in the TMN E2-region lesion rats (Jin et al., 2007). Moreover, it has been found

that histamine content was decreased in amygdala of amygdala kindling-induced focal seizure with secondary generalized seizure (Kamei, Ishizawa, Kakinoki & Fukunaga, 1998). Besides, a reduction of brain histamine level has been found in transauricular kindling rats (Li, Liu, Zhu, Zhou & Chen, 2006), and 6-Hz stimulation mice (Jahan, Pillai & Vohora, 2017). In the audiogenic DBA/2 mice, a decrease of histamine level has been detected in the hypothalamus (Tuomisto, Sturman, Freeman & Tarhanen, 2003). And a decrease of blood histamine level has been found that hyperthermia-induced convulsion in infant rats (Gholipoor, Saboory, Roshan-Milani & Fereidoni, 2013). Histamine levels in the striatum, hippocampus, amygdala, midbrain, thalamus and hypothalamus of genetically epilepsy-prone KM rats were significantly lower than epilepsy resistant Wistar rats (Onodera, Tuomisto, Tacke & Airaksinen, 1992). However, in the KA-induced temporal lobe epilepsy, KA immediately increases brain histamine and histamine immunoreactive nerve fibers in the piriform cortex, amygdala, hippocampus and striatum after KA injection 6 hours later (Lintunen, Sallmen, Karlstedt & Panula, 2005). The reduction of histamine content observed in many brain regions across focal seizure and generalized seizures, suggesting that histamine involves in the pathological process of epilepsy. However, it is still unclear how histamine content change in the different stage of epilepsy.

In histamine receptor level, only H1R and H3R have been found change in epilepsy model. The mRNA expression of H1R transiently decreases in the midline areas and the ventral thalamus, and the mRNA expression of H3R isoforms with a full-length third intracellular loop firstly transiently decrease and increase after 1 week in the ventral posterior, posterior, and geniculate nuclei in the KA model (Jin, Lintunen & Panula, 2005). However, another research reported that KA transiently (after KA injection 6, 12 and 24 hours) increases brain mRNA of H3R isoforms with a full-length third intracellular loop in the hippocampal CA3, followed by piriform cortex and amygdala and then the hippocampal CA1 area (Lintunen, Sallmen, Karlstedt & Panula, 2005). Likewise, the H1R density increases in superior colliculus, central grey, nucleus interpositus and pontine nuclei in the genetic epilepsy-prone WAG/Rij rats (Midzyanovskaya & Tuomisto, 2003). The difference outcome between the former two studies may be caused by different sampling times and different brain regions. For the expression of histamine receptor under epilepsy, more researches are needed to elucidate the changes of histamine receptors, especially H2R and H4R.

*4.2 The therapeutics effect of ligands targeting histamine and histamine receptors on epilepsy in animal mode*l

There are several studies investigating the protective effects of histamine in epilepsy. The histamine precursor, carnosine and histidine showed a protective effect on PTZ kindling rat indicating by seizure onset delay, seizure stage decrease, as well as prolonging latency to myoclonic jerks (Chen, Li, Zhu, Shen & Wei, 2002; Zhang, Shen, Jin, Hu, Zhao & Chen, 2004). Similarly, histidine and histamine inhibit seizure in amygdala kindling rats (Ago, Ishikawa, Matsumoto, Ashequr Rahman & Kamei, 2006; Kamei, Ishizawa, Kakinoki & Fukunaga, 1998), audiogenic seizure (AGS) in GEPR-9s rats (Feng & Faingold, 2000; Feng, Naritoku, Randall & Faingold, 2001), and rhythmic vestibular stimulation epilepsy like mice (Yawata, Tanaka, Nakagawa, Watanabe, Murashima & Nakano, 2004), this effect is attenuated by H1R antagonist, pyrimidine, diphenhydramine and chlorpheiramine (Ago, Ishikawa, Matsumoto, Ashequr Rahman & Kamei, 2006; Kamei, Ishizawa, Kakinoki & Fukunaga, 1998), suggesting H1R medicates anti-seizure effect of histamine. However, Yoshida reported that L-histidine did not reduce seizure ranks and afterdischarge duration (ADD) in amygdaloid kindling rats (Yoshida, Noguchi & Tsuru, 2000). This may be due to the fact that the action of histidine will be affect by its administration dosage. For example, L-histidine prolonged the latency to the onset of bilateral forelimb clonus, without changing the seizure stages and ADD, however, daily treatment of L-histidine facilitated the seizure development (Wada, Shiraishi, Nakamura & Koshino, 1996). Ligands inhibiting the HNMT (thus increasing the brain histamine content), metoprine decreased the seizure stage in amygdala kindling rats and delayed the seizure onset in epileptic-like mice after the vestibular stimulation (Kamei, Ishizawa, Kakinoki & Fukunaga, 1998; Yawata, Tanaka, Nakagawa, Watanabe, Murashima & Nakano, 2004). In addition, metoprine decreased the duration and severity of clonic-tonic convulsions induced by AGS in KM rats and suppressed the spike wave discharge in WAG/Rij rats (Samotaeva, Birioukova, Midzyanovskaya, Kuznetsova, Bazyan & Tuomisto, 2012; Vinogradova, Shatskova & Tuomisto, 2007). These researches suggest preventing histamine degradation could effectively protect against epilepsy.

Next, we discuss the therapeutic effect of several H1R antagonists, including antazoline, cetirizine, chlorpheniramine, cyproheptadine, diphenhydramine, epinastine, ketotifen, loratadine, mepyramine, pyrilamine and triprolidine. In the MES-induced seizure model, antazoline, ketotifen, diphenhydramine, chlorpheniramine, and cyproheptadine show varying degrees of anti-seizure effects in adult mice or 3 weeks infant rats (Ishikawa et al., 2007; Swiader, Wielosz & Czuczwar, 2004), however, the ketotifen accelerates seizure in infant rats has been found in MES-induced seizure model (Yamada, Takizawa, Tamura & Kanda, 2012). The controversial outcome of ketotifen in MES infant rats, might due to the different dosage: orally administrated 5 or 10mg/kg leading positive effect, whereas large dose 30 mg/kg showing the opposite. Similarly, opposite outcomes of H1R antagonists manifesting in the rhythmic vestibular stimulation epilepsy like mice, diphenhydramine at a dosage of 15 mg/kg accelerated this process (Yawata, Tanaka, Nakagawa, Watanabe, Murashima & Nakano, 2004), whereas, diphenhydramine at 30 mg/kg delayed the convulsive seizure induction (Sturman, Freeman & Quinn, 2001). Besides, the H1R antagonist, pyrilamine, ketotifen and diphenhydramine, but not epinastine, loratadine and cetirizine, accelerates seizures in amygdala kindling model (Fujii, Tanaka, Harada, Hirai & Kamei, 2003; Yokoyama, Sato, Iinuma, Onodera & Watanabe, 1996). Additionally, another H1R antagonist, triprolidine increased seizures severity and neuronal damage in the septum, thalamus, CA3 region of the hippocampus, and retrosplenial granular cortex (RGC) in the KA-treated immature mice (Kukko-Lukjanov et al., 2010). Interestingly, the H1R antagonist ketotifen possessed a biphasic action, acutely it enhanced the anticonvulsant action of carbamazepine and phenobarbital while, following 7-day treatment, reduced the antiseizure activity of carbamazepine in MES (Swiader, Wielosz & Czuczwar, 2004). These findings demonstrate the controversial therapeutic effect of H1R antagonist in epilepsy, and the dosage of H1R antagonists might contribute that.

Reports about the ligands targeting H2R in epilepsy are limited. One study showed that an H2R agonist, amthamine decreased clonic-tonic seizure in picrotoxin-induced and PTZ-induced epilepsy mice model (Seeley & Sturman, 2001). Another reported that cimetidine, an H2R antagonist, given alone either acutely or chronically did not alter PTZ-induced seizure and also did not affect the anticonvulsant properties of AEDs, such as valproate, clonazepam or phenobarbital in PTZ model. (Swiader, Porebiak, Swiader, Wielosz & Czuczwar, 2006). Although potential positive therapeutics obtained from H2R agonist, systemic investigations are urge to reveal the role of H2R in epilepsy.

Up to date, many H3R ligands have been synthesis to target epilepsy. H3R antagonist, clobenpropit, thioperamide, and E177 delayed seizure onset, seizure stage, and prolonged the latency to myoclonic jerks and clonic generalized seizure in PTZ-induced seizure model (Alachkar et al., 2020; Zhang et al., 2003; Zhang, Chen, Chen, Hu & Ding, 2013; Zhang, Shen, Jin, Hu, Zhao & Chen, 2004). Similar to PTZ model, there are many H3R antagonist ligand, including thioperamide, iodophenpropit, AQ0145, clobenpropit, VUF5514, VUF5515 and VUF4929 decreased seizure stage in amygdala kindling model, except AQ0145, all ligands also showed protective effect in MES model (Harada, Fujii, Hirai, Shinomiya & Kamei, 2004; Harada, Hirai, Fujii, Harusawa, Kurihara & Kamei, 2004). The H3R antagonists DL77 showed anticonvulsant effect in MES-induced seizure, and the anticonvulsant effect of DL77 in MES model was reversed by H1R antagonist pyrilamine (Sadek, Saad, Subramanian, Shafiullah, Łażewska & Kieć-Kononowiczc, 2016), suggesting the action is H1R-dependent. Besides, in the rhythmic vestibular stimulation epilepsy like mice, H3R antagonist thioperamide decreased the induction of seizure (Yawata, Tanaka, Nakagawa, Watanabe, Murashima & Nakano, 2004). Furthermore, different degree of antiepileptic and anticonvulsant effects of novel non-imidazole H3R antagonist ligands have been found in PTZ, STR and MES-induced seizure model (Alachkar et al., 2018a; Alachkar et al., 2018b; Bastaki, Abdulrazzaq, Shafiullah, Wiecek, Kieć-Kononowicz & Sadek, 2018; Sadek et al., 2014a; Sadek et al., 2016; Sadek, Saad, Schwed, Weizel, Walter & Stark, 2016; Song, Yan, Zhang, Guo, Zhou & Deng, 2020). H3R antagonist, ABT-239, delayed onset of seizure and reduced behavioral seizures and restored altered expression of Bax, cleaved caspase-3, phospho-Akt (Ser473) and CREB in KA mice (Bhowmik, Saini & Vohora, 2014). Another H3R antagonist E177, also shows protective effect in pilocarpine induced statue epilepticus rat indicating by increasing the survival rate and prolonging latency to the first seizure, and this effect was blocked by H3R agonist R-(α)-methylhistamine and H2R antagonist zolantidine, but not H1R antagonist pyrilamine (Alachkar et al., 2019). Moreover, the H3R naphthalene derivatives

compound 13 also shows protective effect of seizure in PTZ and 6-Hz stimulation model (Łażewska et al., 2018). It needs to note that the H3R naphthalene derivatives compound 13 was accepted by the National Institute of Neurological Disorders and Stroke/National Institutes of Health (NINDS/NIH; Rockville, MD, USA) started an Anticonvulsant Screening Program (ASP) (Łażewska et al., 2018). This compound 13 shows the possibility to enter clinical trials and be marketed as pitolisant. Betahistine, an H1R agonist/H3R antagonist shows good protective effect indicating by preventing generalized tonic-clonic seizures induction and diminishing forelimb clonic seizures intensity in PTZ treated mice (Yazdi, Doostmohammadi, Pourhossein Majarshin & Beheshti, 2020). Betahistine reduced ADD without changing the seizure ranks in amygdaloid kindling rats (Yoshida, Noguchi & Tsuru, 2000).

The PTZ induced epileptic seizure model usually accompanied by learning and memory deficits, which can be rescued by L-histidine (Chen, Ren, Zhang & Hu, 2012; Zhang, Ma & Li, 2006), and H3R antagonist, thioperamide, JNJ-5207852, and E177 (Alachkar et al., 2020; Jia et al., 2006; Zhang, Chen, Chen, Hu & Ding, 2013), and this effect of L-histidine might through H2R but not H1R (Zhang, Chen, Chen, He & Hu, 2017). Histidine promotes the anticonvulsant efficacy of carbamazepine and ameliorates the memory deficits induced by chronic transuricular kindled seizure (Li et al., 2005; Li, Liu, Zhu, Zhou & Chen, 2006).

Although, in most cases, H3R antagonists/inverse agonists show good anti-seizure effects in different epilepsy models. The negative outcome also has been found in non-imidazole H3R antagonists/inverse agonists containing triazole moiety in PTZ mice (Song, Yan, Zhang, Guo, Zhou & Deng, 2020), and the non-imidazole H3R antagonists DL77 in STR rat (Sadek, Saad, Subramanian, Shafiullah, Łażewska & Kieć-Kononowiczc, 2016). The H3R antagonist, thioperamide shows no effect on seizure ranks and ADD in amygdaloid kindling rats (Yoshida, Noguchi & Tsuru, 2000). Whether histamine-independent signaling is involved in the anti-seizure effect of H3R antagonists/inverse agonists is still unknown.

4.3 The genetic and other therapeutics effects of targeting histamine and histamine receptors on epilepsy in animal model

Since histamine and its precursor L-histidine, as well as most H3R antagonists obtain positive outcomes. As pharmacological modulation is often associated with non-specific effect, genetically intervention can address the precise role of central histaminergic signaling epilepsy more specifically.

The H1R-KO mice showed more severe seizures with correlation of neuronal damage in the thalamus and RGC in P9 immature mice (Kukko-Lukjanov et al., 2010). Those authors then described the age-dependent susceptibility of H1R-KO mice to seizure-induced by KA administration: P14 H1R-KO mice showed no changes; P21 KO mice decreased survival rate with more severe seizures and enhanced neuronal damage in various brain regions; P60 KO mice increased the neuronal damage without changing the seizure severity (Kukko-Lukjanov et al., 2012). In the HDC-KO mice, the hyperthermia-induced febrile seizure was more severe that wide type (WT) mice (Dai et al., 2015). These findings indicate that deletion of H1R and HDC increases the susceptibility of epilepsy.

Based on the above researches results, it can be basically concluded that the central histaminergic signaling participates in epilepsy. Most importantly, the H3R antagonist shows powerful anti-epileptic and anticonvulsant effects in many epileptic animal models. The protective effect of H3R antagonist works mainly through H1R. However controversial opinion still exists (Alachkar et al., 2019; Sadek, Saad, Subramanian, Shafiullah, Łażewska & Kieć-Kononowiczc, 2016). What's more, the action of H1R antagonists in seizure animal model also not consistent. The incomplete understanding of these issues needs further studies to investigate.

5. Perspectives and Conclusion

Current evidence from available clinical and preclinical studies supports that histamine and histamine receptor involves in the pathogenesis of epilepsy. There are still numerous unsolved issues left behind.

5.1 What is the role of other histamine receptors in epilepsy?

H1R and H3R expression have been merely detected in one type of epilepsy animal model. The changes of histamine receptors need systemic animal researches and autopsy studies to elucidate further, especially H2R and H4R. In addition, H1R, H2R and H3R antagonists have been investigated in many epilepsy animal model, however, the report of H4R in epilepsy is still missing. Even the H4R shows the potential in regulating neuronal excitability (Desmadryl et al., 2012). Investigations should be implemented to detect the distribution and expression of H4R in epilepsy animal, and applying H4R agonists and antagonists to epilepsy intervention. What' more, some studies found that action of H3R ligands relies on H1R or H2R, the specific histamine receptor KO mice are available to ensure the action of H3R antagonist through H1R or H2R.

Even the H3R antagonists receive a lot of attention upon its desirable anti-epileptic and anticonvulsant effects, the action manner of H3R antagonists is not fully understood. As H3R is identified as either autoreceptor or heteroreceptor, it may be very complex about how it regulates neural excitability and thus related in epilepsy. For example, it is still largely unknown whether histamine-independent signaling is involved in the anti-seizure effect of H3R antagonists/inverse agonists. In the cerebral ischemia/reperfusion injury, the H3R antagonists protect against the ischemia injury in a histamine independent manner by directly recruiting binding of CLIC4 with H3R (Yan et al., 2014). Whether the action of H3R antagonist is the same in epilepsy that is unclear. HDC inhibitors and HDC-KO animal are regarded as a good choice to answer this question.

5.2 What is the neuronal circuit basis of histaminergic system in epilepsy?

According to the electrographic feature, the epileptic seizure is usually composed of a beginning, a middle and an end, which is associated with seizure initiation, propagation, and termination (Bertram, 2013). There are different neural networks involved in each stage (Wang & Chen, 2019). It is well known that the histaminergic fibers widely project in the brain. Histaminergic system participates in particular one period or the whole process is obscured. Given an example, the nucleus of solitary tract shows an promising neuroprotective role in patients with poorly controlled epilepsy (Cakmak, 2006). It has reported that the histaminergic input from TMN to the solitary tract nucleus participating in arterial pressure regulation (Yamanaka, Gouraud, Takagishi, Kohsaka, Maeda & Waki, 2017). Whether the TMN-solitary tract histaminergic projection regulates epilepsy needs validate further.

Interestingly, although histamine and several histamine receptors receive positive response in epileptic seizure, DBS directly on TMN showed a dominant protection accompanying with a prominent increase of histamine release in the frontal cortex after TMN stimulation in PTZ rats (Nishida, Huang, Mikuni, Miura, Urade & Hashimoto, 2007). However, LFS of the TMN had no appreciable effects in PTZ model (Wu et al., 2008). LFS of the TMN accelerated seizure stage and increased the mean afterdischarge duration (ADD) during acquisition but had no anticonvulsive effect in fully kindled, HFS and bilateral lesions of TMN exacerbated the seizure progression in the amygdaloid kindling (Wu et al., 2008). These finding supports that DBS on TMN is not a good therapeutic approach to control seizure. Advanced technologies, such as novel optogenetics (Kim, Adhikari & Deisseroth, 2017), in combination with novel viral tracing system (Nectow & Nestler, 2020; Xu et al., 2020), provide high temporal and spatial specificity to reveal the circuit basis of histaminergic system in epilepsy.

5.3 What is the cellular and molecular mechanism of histaminergic system in epilepsy?

The imbalance of excitatory glutamatergic and inhibitory GABAergic neurons is considered as the classical theory for epilepsy. The action of histamine is localized in histaminergic neurons or innervating to glutamatergic or GABAergic neurons which is not fully understood. The well development of transgenic mice, such as HDC-Cre, CamKIIα-Cre, and Vgat-Cre are available to neuronal specific modulation with the help of optogenetic. H3R acts as heteroreceptor which regulates other neurotransmitters synthesis and release. In the cultured cortical neurons, the H3R antagonist clobenopropit effectively reduced the NMDA-induced neuronal toxicity by increasing GABA releases through cAMP/PKA signaling pathway (Dai et al., 2007).Whether other neurotransmitters, such as glutamate, GABA, acetylcholine and 5-HT participating in the action of H3R needs to identify further. Voltage-gated ion channels including Na^+, Ca^{2+} and K^+

channels, contribute to the generation of seizure discharges (Catterall, 2014; van Loo et al., 2019; Wei et al., 2017; Yuan & Isom, 2014). Whether histamine or its receptor regulate voltage-gated ion channels activity in epilepsy needs further evaluation. Since cellular single RNA sequencing with high efficiency (Lein, Borm & Linnarsson, 2017), that provides a convenient way to investigate the molecular mechanism.

In conclusion, plenty of evidence suggested the histamine and its receptor are involved in epilepsy. The discovery of the central histaminergic system broadens the AED development aspects, especially for H3R antagonists. Nevertheless, there are many questions unsolved. A precise understanding of the role of the central histaminergic system in epilepsy at molecular, cellular, or even neural circuit level is encouraged to clinical transformation in epilepsy therapeutics.

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Conflict of interests

The authors declare that there are no conflicts of interest.

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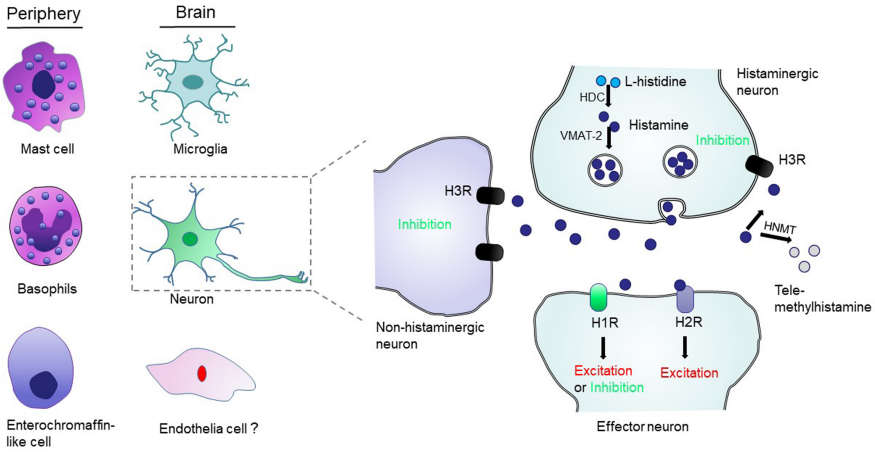
Figure legend

Figure 1. Histamine biosynthesis process and histamine receptors distribution and induced effects.

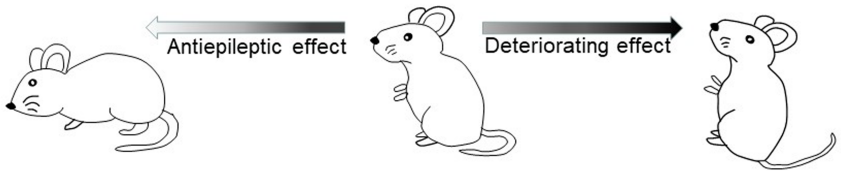
In the brain, the tuberomamillary nucleus neurons is the main source of histamine. Moreover, microglia also give rise to synthesize histamine, while histamine produced from cerebrovascular endothelial cells is controversial (shown in the middle). In the peripheral tissue, the mast cells and basophils in the immune system common synthesize histamine. Besides, the enterochromaffin-like cells in stomach also show the possibility to synthesis histamine (shown in the left). L-histidine was decarboxylated by HDC into histamine. Neuronal histamine was packaged into vesicles VMAT-2, and calcium release evokes histamine release from vesicles into the postsynaptic cleft, which is metabolized into tele-methyhistamine by HNMT. There are 4 histamine receptors distributed in the brain, post-synaptical H1R mediating neuronal excitation or inhibition, post-synaptical H2R facilitating neuronal excitability, and pre- or post- synaptical H3R inhibiting neuronal excitability, as well the H4R exciting neurons which is not expressed in neurons.

Figure 2. The changes of histamine in epilepsy and therapeutic effects of histamine related ligands on epilepsy.

A summary of the histamine and histamine receptor have been identified in epilepsy to date (shown in the upper). The arrow indicates up- or down-regulation, "-" indicates no change. The effect of related histamine ligands on epilepsy (shown in the lower).



acute	chronic
Histamine(↑ or -), H1R(↓)	Histamine(↑), H1R(↓), H3R(↑ or↓)



Antiepileptic	No effect	Deteriorating
Histamine, L-histidine, HNMT inhibitor H1R/H3R antagonist H2R agonist H1R agonist/ H3R antagonist	H1R/H2R/H3R antagonist	L-histidine, H1R antagonist

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