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REVIEW ARTICLE

Isoforms of the human histamine H_3 receptor: Generation, expression in the central nervous system and functional implications

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Abstract

Histamine plays a significant role as a neuromodulator in the human central nervous system. Histamine-releasing neurons are exclusively located in the tuberomammillary nucleus of the hypothalamus, project to all major areas of the brain, and participate in functions such as the regulation of sleep/wakefulness, locomotor activity, feeding and drinking, analgesia, learning, and memory. The functional effects of histamine are exerted through the activation of four G protein-coupled receptors (H1, H2, H3 and H4), and in the central nervous system the first three receptors are widely expressed. The H3 receptor (H3R) is found exclusively in neuronal cells, where it functions as auto- and hetero-receptor. One remarkable characteristic of the H3R is the existence of isoforms, generated by alternative splicing of the messenger RNA. For the human H3R, 20 isoforms have been reported; although a significant number lack those regions required for agonist binding or receptor signaling, at least five isoforms appear functional upon heterologous expression. In this work we review the evidence for the generation of human H3R isoforms, their expression, and the available information regarding the functionality of such receptors. (Gac Med Mex. 2016;152:82-90)

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Introduction

Histamine participates in numerous functions in the human body, such as allergic responses, acid gastric secretion, synaptic transmission modulation and immune response, by activation of 4 calcitonin gene related peptide (GPCR) subtypes[1-5]: H_1, H_2, H_3 and H_4.

In the central nervous system (CNS), there is a group of histaminergic neurons (64,000 cells in total), located in the tuberomammilar nucleus of the posterior hypothalamus, which send projections to the brain, the cerebellum and the spinal chord[6,7], with the highest innervation density in the cerebral cortex, basal ganglia, the thalamus, the hypothalamus and the hippocampus[7,8].

Histamine acts as a neuromodulator in the CNS, facilitating or inhibiting neuronal activity[9], and participates in processes such as the sleep-wake cycle, motor activity, water and food ingestion, nociception and memory and learning. Three of the 4 histamine receptors,

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H_1, H_2 and H_3, are widely expressed in the CNS[9,10]; and the H_3 receptor (H_3R) is exclusively expressed in neuronal cells, both at the CNS and the peripheral nervous system. In the CNS, H_3R is found in the histaminergic neurons themselves as an autoreceptor and in neurons that release other neurotransmitters (heteroreceptor). An important feature of H_3R is the existence of isoforms, generated by precursor mRNA alternative splicing. In the case of hH_3R, 20 isoforms have been reported and, although some lack the necessary regions for agonist-binding or the domains involved in signaling, at least 5 are functional when expressed on heterologous systems.

In this work, the structure and function of hH_3R are briefly described, and subsequently, available information on the described isoforms is reviewed with regard to their structure, their expression in the CNS, their pharmacological and functional features and their possible relationship with specific brain functions.

H_3R

H_3R was pharmacologically identified in 1983 as the autoreceptor responsible for histamine synthesis and release negative feedback[11,12]. As a heteroreceptor, H_3R modulates the release of noradrenalin, serotonin, dopamine, glutamic acid, gamma-aminobutyric acid (GABA) and neuropeptides such as substance P and CGRP[9,13].

There are evidences of H_3R post-synaptic localization in certain regions of the brain, such as the neostriatum, cerebral cortex, the hippocampus and the nucleus accumbens[14,15]. In striatal GABA-ergic neurons, post-synaptic H_3Rs form heterodimers with dopamine receptors D_1 and D_2 by modulating their signaling, with relevant implications for locomotor activity[16-19]. In the primary culture of cerebral cortex neurons of the mouse, H_3R activation increases the expression of anti-apoptotic proteins and partially protects the cells from damage induced by serum deprivation or by activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) type[20].

Structural make-up

H_3R is a seven-transmembrane domain (TM) protein, which originates three extracellular and three intracellular loops of different sizes. The third intracellular loop (i3) and the terminal carboxyl region are important for the coupling of the receptor to G-proteins and the ensuing intracellular signalling[21-23].

Intracellular signaling

H_3R is coupled to $Ga_{i/o}$ proteins, which trigger several intracellular signaling pathways, including the following:

- Cyclic adenosine 3'-5'-monophosphate (cAMP) formation inhibition.
- Phospholipase A_2 activation.
- Voltage-activated Ca^{2+} channels (N and P/Q) opening inhibition, which underlies the inhibitory effect on neurotransmitter release.
- Phosphatidylinositol 3-kinase (PI3K) pathway activation.
- Activation of mitogen-activated protein kinases (MAPK).
- Activation of phospholipase C, leading to Ca^{2+} mobilization from intracellular storages.
- Na^+/H^+ exchange inhibition.
- Activation of inward rectifier K^+ channels[24-26].

Generation of H_3R isoforms by mRNA alternative splicing

A single gene can potentially codify for several proteins by mRNA alternative splicing. In this process, exons or introns can be excluded from precursor mRNA, thus generating different variants of mature mRNA. The end-result is the synthesis of several proteins from a same gene, with different amino acid sequence and, therefore, different potentials in their structural and functional properties. mRNA alternative splicing can also lead to the presence of one premature stop codon, resulting in a smaller-size protein.

The existence of H_3R isoforms was initially suggested in several mammal species (guinea pig, rat, mouse, monkey and human) due to pharmacological heterogeneity of H_3Rs of different cerebral areas, as shown by radioligand-binding and functional assays[27-33]. In 1999, complementary DNA (cDNA) cloning by Lovenberg et al. allowed for molecular study of the receptor, which showed that the corresponding gene is found on the long arm of chromosome 20 (20q13.32-20q13.33) and that cDNA codifies for a 445-amino acid (aa) protein[3]. Nucleotide sequence analysis shows that the gene contains 3 introns (Fig. 1) localized at the same position in the rodents' gene and that the regions contiguous to sequence-deletion and isoform-generation sites contain alternative splicing donor and acceptor sites, also present in homologous genes of the mouse and the guinea pig[27,29,34,35].

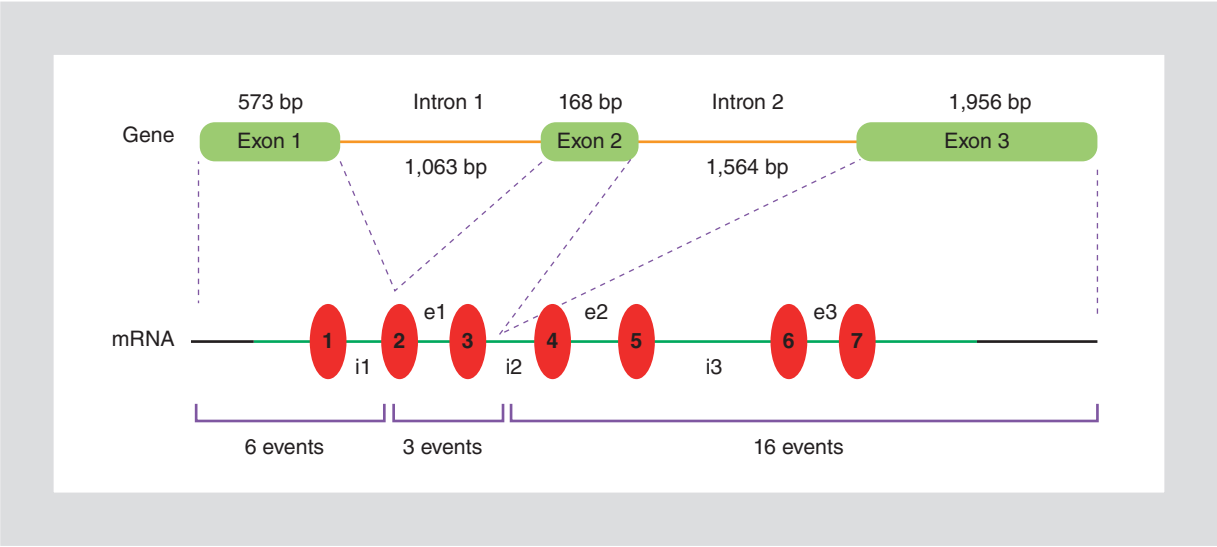

Figure 1. *hH_3R genomic organization. In the schematic representation of the hH_3R gene, exons (green) and introns (brown lines), whose extension is expressed in base pairs (bp), are shown. In the schematic representation of the hH_3R mARN, the codifying region (green line) is shown with the TM domains depicted as red ovals, and the extra- and intracellular loops are indicated. The black line indicates the non-transduced region. The mRNA regions where alternative splicing events take place and their number are indicated by the brackets.*

The reverse transcription polymerase chain reaction (RT-PCR) analysis has so far enabled identifying 20 hH_3R isoforms, with differences in the amino- and carboxyl-termini length, loss of amino acids in the third intracellular loop (i3) and sequence deletions on TM regions (Fig. 2). Of them, eight isoforms (hH_3R_{445}, hH_3R_{453}, hH_3R_{415}, hH_3R_{413}, hH_3R_{409}, hH_3R_{373}, hH_3R_{365} and hH_3R_{329}) are able to bind ligands when expressed in heterologous systems. These isoforms are homologous in their TM regions, and differ in the amino- and carboxyl-termini regions and/or i3 loop. The other 12 isoforms do not bind ligands and, therefore, would render non-functional, although in several cases their activity has not been studied in detail.

hH_3R isoforms are generated by deletion and/or retention mechanisms of a pseudo-intron, which in the human and the rat occur primarily at the mRNA sequence corresponding to the gene's exon 3[28,35]. A similar mechanism has been reported for other receptors also coupled to $Ga_{i/o}$ proteins, such as dopamine D_2 and D_3, type B GABA and type μ opioid receptors[36-39].

hH_3R isoforms

The hH_3R alternative splicing events occur in four mRNA regions, three of them located at regions corresponding to amino acids 7-42, 85-98 and 197-417 of the protein (Fig. 2), whereas in the fourth region, the events generate isoforms with 8 additional aa on the carboxyl-terminus extreme (Fig. 2)[40].

Using human thalamus mRNA, Cogé et al., in 2001[41], cloned the 445 aa hH_3R (hH_3R_{445}) and five different isoforms of 431, 415, 365, 329 and 326 aa, which show amino acid elimination on the TM2 region (hH_3R_{431}) o the i3 loop (hH_3R_{415}, hH_3R_{365}, hH_3R_{329} and hH_3R_{326}). That same year, Tardivel-Lacombe et al.[35] confirmed the presence of the hH_3R_{445} isoform in the human brain and detected another receptor with deletion of a 32 aa fragment (aa 274-305) on the i3 loop (hH_3R_{413}) (Table 1). Also in 2001, Tsui described two additional isoforms of the receptor (hH_3R_{351} and hH_3R_{340}) (Table 1)[42], generated by the combination of alternative splicing events, consisting in the absence of amino acids 85-98 or 393-417, in addition to the i3 loop alternative splicing event that gives rise to the 365 aa receptor by eliminating 240 nucleotides[41].

Nakamura et al., in 2002[44], identified yet another hH_3R isoform, with 8 additional aa at the carboxyl terminus extreme of the receptor (hH_3R_{453}) (Table 1), generated by the presence of an alternative splicing donor site in the sequence of the transduction stop codon and of a new alternative splicing acceptor site located at the original cDNA non- extreme 3' codifying region.

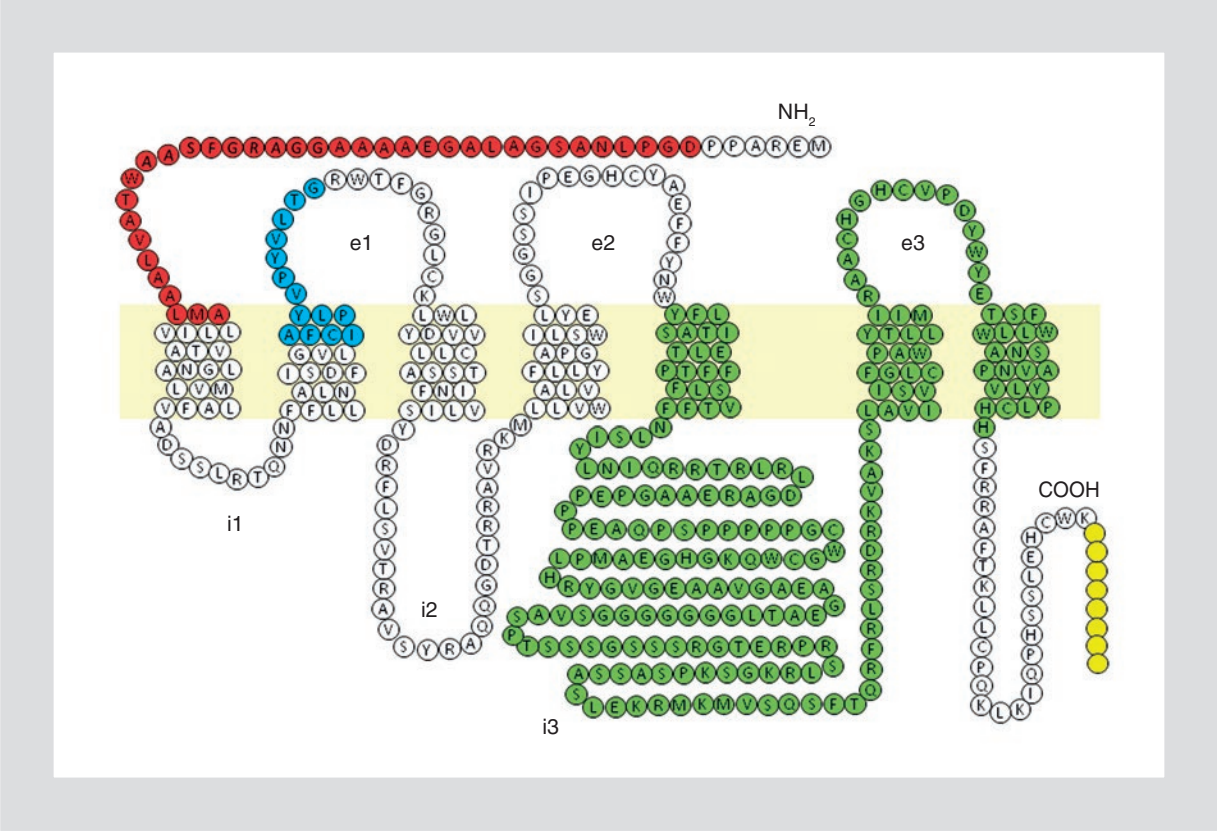

Figure 2. *Regions where hH_3R alternative splicing takes place. The events occur in four different regions, three of them located at positions corresponding to amino acids 7-42 (red), 85-98 (blue) and 197-417 (green). In the fourth region, the events generate isoforms consisting of 8 additional aa at the carboxyl-terminus extreme (yellow).*

Combined alternative splicing events have been reported that originate four additional hH_3R isoforms[45]:

- hH_3R_{301}, generated by deletion of 144 aa with loss of large part of i3 loop, as well as of regions TM6 and TM7 of the protein.
- hH_3R_{373}, with the elimination of 80 aa in i3 loop reported for isoform hH_3R_{365}[41], and a second alternative splicing site located after the stop codon in the codifying sequence, which removes the codon and entails 8 additional aa at the carboxyl-terminus region.
- hH_3R_{309}, with deletion of 408 nucleotides, originating a receptor without the TM4 and TM5 regions and part of i3 loop.
- hH_3R_{221}, with an identical splicing event to that of hH_3R_{301}, as well as the event observed for the hH_3R_{373} isoform i3 loop, which originates a receptor with only 5 TM.

Gallagher and Yates, in 2007[46], described 6 more isoforms obtained from human brain tissue mRNA. One of them, hH_3R_{409}, consists in the loss of 36 aa (aa 7-42) of hH_3R_{445} amino-terminus region of. The other isoforms are generated by the previously reported alternative splicing events combination. A 329 aa isoform, hH_3R_{329}, is generated by the loss of amino acids 7-42 at the amino-terminus region and 80 aa in the i3 loop, the latter described for isoform hH_3R_{365}[41]. Another isoform, hH_3R_{395}, involves the aforementioned elimination of amino acids 7-42 and an additional loss of 14 aa at the TM2 region, important for the ligand to bind to the receptor and, therefore, for its activation. The three last reported isoforms show variable amino acid elimination at the i3 loop (30, 116 and 119 aa), in addition to the absence of 36 aa at the amino-terminus extreme of the protein, thus generating the hH_3R_{379}, hH_3R_{293} and hH_3R_{290} receptors (Table 1).

hH_3R isoforms expression in the CNS

The analysis performed by Cogé et al.[41] on the expression in human CNS of mRNA of the 6 isoforms cloned by this group (hH_3R_{445}, hH_3R_{431}, hH_3R_{415}, hH_3R_{365},

Table 1. hH_3R isoforms expression in human brain and signaling in heterologous systems

Isoform	Expression in the brain	Signaling
$H_3(445)$	Thalamus, neostriatum, cortex, cerebellum. amygdala, substantia nigra, hippocampus, hypothalamus, corpus callosum, spinal chord	↓ cAMP, ↑ MAPK, [^{35}S]-GTPgS binding, ↑ [Ca^{2+}]i
$H_3(431)$	Amygdala, cerebellum, neostriatum, thalamus, prefrontal cortex	Not determined
$H_3(415)$	Neostriatum, thalamus, cerebellum, amygdala	↑ [Ca^{2+}]i
$H_3(365)$	Cerebellum, thalamus, hypothalamus, neostriatum, substantia nigra, hippocampus, amygdala, prefrontal cortex	↑ [Ca^{2+}]i, ↓ cAMP, [^{35}S]-GTPgS binding
$H_3(329a)$*	Substantia nigra, amygdala, cortex, hypothalamus	Non-functional
$H_3(326)$	Substantia nigra, prefrontal cortex, amygdala, hypothalamus	Not determined
$H_3(413)$	Neostriatum, amygdala	Not determined
$H_3(453)$	Not determined	↓ cAMP
$H_3(301)$	Not determined	Non-functional
$H_3(373)$	Hippocampus, substantia nigra, amygdala, hypothalamus	↓ cAMP
$H_3(309)$	Not determined	Non-functional
$H_3(221)$	Not determined	Not determined
$H_3(409)$	Not determined	Not determined
$H_3(329b)$*	Not determined	Not determined
$H_3(395)$	Not determined	Not determined
$H_3(379)$	Not determined	Not determined
$H_3(293)$	Not determined	Not determined
$H_3(290)$	Not determined	Not determined
$H_3(351)$	Not determined	Not determined
$H_3(340)$	Not determined	Not determined

*Isoforms hH_3R_{329a} and hH_3R_{329b} have the same amino acid number, but differ on the nucleotide elimination region.
↑: increase; ↓: decrease; [Ca^{2+}]i: calcium intracellular concentration.
Adapted from Lovenberg et al.[3], Bongers et al.[32], Tardivel-lacombe et al.[35], Bongers et al.[40], Cogé et al.[41], Tsui[42], Nakamura et al.[43], Wiedermann et al.[44], Wellendorph et al.[45] and Gallagher et al.[46].

hH_3R_{329} and hH_3R_{326}) showed that isoform hH_3R_{445} was the most abundant and, at the same time, high expression of isoforms hH_3R_{415} and hH_3R_{365} was detected at the thalamus, caudate nucleus and cerebellum, where isoforms hH_3R_{329} and hH_3R_{326} levels were very low. In contrast, isoforms hH_3R_{329} and hH_3R_{326} mRNA expression was high at the amygdala, substantia nigra, cortex and hypothalamus, with no evidence of expression at the hippocampus (Table 1). In the study by Wellendorph et al. (2002)[45], hH_3R_{445} mRNA was found in the hippocampus, basal ganglia, substantia nigra, amygdala and hypothalamus, but not in the thalamus or hindbrain. The same pattern was observed for hH_3R_{365}/hH_3R_{373} receptors mRNA, with the exception that signaling at the hypothalamus was higher for this mRNA.

Esbenshade et al (2006)[31] reported variable hH_3R_{445}, hH_3R_{413}, hH_3R_{365} and hH_3R_{329} isoforms mRNA levels in human brain tissue; isoforms hH_3R_{445} and hH_3R_{365} were the most abundant, with the highest levels in the hypothalamus and cerebellum, and similar expression on the amygdala, caudate nucleus, substantia nigra, thalamus and cerebellum. Isoforms hH_3R_{413} and hH_3R_{329} were much less abundant; isoform hH_3R_{413} was detected only in the caudate nucleus and the amygdala, and receptor hH_3R_{329}, only in the amygdala.

Bongers et al.[32] compared the 445 and 365-aa isoforms mRNA expression in the human cerebellum

and reported the following: high expression of hH_3R_{445} in the cerebellum and caudate nucleus, moderate expression in the hypothalamus and thalamus, low expression in prefrontal cortex, amygdala, hippocampus, corpus callosum and substantia nigra, and very low expression in the spinal cord. Isoform hH_3R_{365} was detected in the same regions with higher expression (1.4-fold) than that of hH_3R_{445}, except for the caudate nucleus, corpus callosum and spinal cord, areas where isoform hH_3R_{445} expression was 3.5, 2.8 and 2.2-fold with regard to that for receptor hH_3R_{365}.

hH_3R isoforms pharmacological and functional characteristics

To date, H_3R isoforms pharmacological and functional characteristics have been only evaluated by means of their expression on cell lines.

Expression in NIH-3T3 cells together with reporter gene assays involving cAMP formation inhibition, showed that hH_3R_{445}, hH_3R_{365} and hH_3R_{373} receptors were functional, whereas isoforms hH_3R_{301} (lacking most part of i3 loop, as well as TM6 and TM7 regions) and hH_3R_{309} (lacking TM4 and TM5 regions, and part of the i3 loop) were not[45]. Isoform hH_3R_{221} functionality was not analyzed, with only 5 TM regions and loss of 80 aa at the i3 loop. In the same study, the response to different agonists showed that they were 5-27-fold more potent to activate isoform hH_3R_{365} than isoform hH_3R_{445}. By contrast, selective antagonists were 5-6-fold less potent for isoform hH_3R_{365} than for isoform hH_3R_{445}.

The isoform with 8 additional aa at the carboxyl-terminus extreme of the receptor (hH_3R_{453}) showed ligand binding when expressed in COS-7 cells, and in HEK-293 cells, this receptor inhibits cAMP formation when activated by histamine agonists, N-a-methylhistamine (NMHA), R-α-methylhistamine (RAMH) and imetit, with a mean effective concentration (EC_{50}) of 19, 0.26, 0.71 and 1,7 nM, respectively[43].

In rat glioma C6 cells, isoforms hH_3R_{445}, hH_3R_{415} hH_3R_{365} and hH_3R_{329} showed similar affinity for the [^{3}H]-NMHA marked agonist, with dissociation constants (Kd) of 0.50, 1.0, 0.25 and 0.63 nM, respectively[31]. In the same work, the calcium mobilization analysis in HEK cells transfected with Ga_{qi5}, coupled to phospholipase C stimulation and whose last 5 aa correspond to the sequence of $Ga_{1/o}$ proteins, which enables for them to be activated by H_3R, showed functional responses to the RAMH agonist with similar potency for isoforms hH_3R_{445}, hH_3R_{415} and hH_3R_{365} (EC_{50} of 7.9, 5.0 and 7.9 nM, respectively), whereas isoform hH_3R_{329} did not render functional. With regard to maximum response, isoform hH_3R_{415} effect was 60% of hH_3R_{445} response, and isoform hH_3R_{365} response was lower than 10%.

In 2007, Bongers et al.[32] reported a detailed comparison of isoforms hH_3R_{445} and hH_3R_{365} pharmacological and functional characteristics. The analysis of [^{3}H]-NMHA binding to isoforms expressed in C6 glioma cells inhibition by 27 ligands showed higher affinity of hH_3R_{365} (3.4-fold on average) for agonists such as histamine itself, immepip and imetit. This difference was even larger (55-fold on average) when a second radioligand, [^{125}I]-iodophenpropit, was used. In contrast, isoform hH_3R_{445} showed higher affinity for H_3R antagonists/reverse agonists, such as ciproxifan, clobenpropit and A-331440. H3R can have spontaneous or constitutive activity[47,48], defined as receptor activation in the absence of agonists. This characteristic results in tonic intracellular signaling, and in the rat's CNS, H_3Rs constitutive activity inhibits histamine synthesis and release in a tonic manner, as well as histaminergic neurons excitability[7,48-52]. Constitutive activity can be reduced o abolished by drugs that bind to the receptor and stabilize it at a state of lower or no activity (inverse agonists).

In the study by Bongers et al.[32] isoforms hH_3R_{445} and hH_3R_{365} functionality was analyzed with [^{35}S]-GTPγS binding assays, indicative of G-proteins activation by the receptor (in HEK cells) and cAMP formation inhibition (in C6 cells). For [^{35}S]-GTPγS binding, agonists were more potent (4.6-fold on average) with isoform hH_3R_{365}. However, maximum effect was higher with isoform hH_3R_{445} (220 and 120% from baseline binding for isoforms hH_3R_{445} and hH_3R_{365}, respectively). In this assay, reverse agonists were more potent (2.6-fold) with isoform hH_3R_{445}. To inhibit forskolin-induced cAMP formation, agonists were more potent (35-fold on average) with isoform hH_3R_{365}, but more efficacious with receptor hH_3R_{445} (80% inhibition compared with 44% for isoform hH_3R_{365}). Conversely, reverse agonists were more potent (14-fold) with isoform hH_3R_{445}, but efficacy was higher with isoform hH_3R_{365}, indicating higher constitutive activity of the shorter isoform. The application of the agonist-receptor-protein G interaction ternary cubic model indicated that isoform hH_3R_{365} higher spontaneous activity would also explain the higher potency and affinity of agonists with this isoform, as well as the lower potency and affinity of reverse agonists.

hH_3R isoforms expression possible functional implications

Histamine participates in the regulation of different cerebral functions. Differential expression of H_3R isoforms in human and rat CNS (Table 1) suggests the possibility of isoforms selective actions in the regulation of these functions. For example, in rodents, primates and humans, there is isoform hH_3R_{445} abundant expression at limbic regions such as the hippocampus, the amygdala and the basal forebrain, suggesting an involvement of this isoform in cognitive and affective states modulation[3,33,34,45]. This isoform is also predominant in the thalamus and the cortex, both cerebral regions that are part of the cortex → basal ganglia → thalamus → cortex circuit, which is critical to motor behavior control[26]. Isoform hH_3R_{445} significant expression at the cortex and hippocampus, both important regions for cognitive functions, suggests its participation in these processes as well.

Bongers et al.[32] showed that isoform hH_3R_{365} is abundantly expressed in the thalamus and the cerebellum, which suggests its involvement in the modulation of synaptic information originating in the basal ganglia circuit and, therefore, in the regulation of motor behavior, e.g., by inhibiting glutamate release[53] from thalamocortical and thalamostriatal terminals[53]. In comparison with the 445-aa isoform, hH_3R_{365} is abundantly expressed at the hypothalamus, where histaminergic neurons are located and, therefore, this isoform could be the main executor of the autoreceptor function and modulate the synthesis and release of histamine itself, as well as the frequency of histaminergic neurons triggering. In this sense, the 413 aa receptor in the rat appears to play an autoreceptor role[54]. Isoform hH_3R_{365} has high constitutive activity[32] and, therefore, it could be also responsible for the tonic inhibition observed in the triggering frequency of histaminergic neurons, where tioperamide, an antagonist/reverse agonist, increases this frequency[48,52].

Isoforms hH_3R_{445} and hH_3R_{365} mRNA is abundant in the neurostriatum, where at least 95% of the neuronal population corresponds to medium spiny neurons of GABAergic nature, in turn divided into two populations that send their axons to the substantia nigra pars reticulata (direct route) or globus pallidus (indirect route)[26]. One of the highest expressions of H_3R is also observed in the neostriatum[14] and, in the medium spiny neurons, the receptor modulates dopamine effects both at the somatic level[16-19] and in synaptic terminals, where it inhibits GABA release[55]. Consequently, it is of interest to determine if both populations express both H_3R isoforms or if these are segregated in neuronal populations, as observed for dopamine receptors, whose D_1 and D_2 receptors are expressed predominantly in striatonigral and striatopallidal neurons, respectively[26].

Drutel et al.[28] showed that two short isoforms of the rat (hH_3R_{413} and hH_3R_{397}) show higher potency to inhibit cAMP formation, whereas the 445 aa isoform is more potent to induce MAPK pathway activation, which, together with hH_3R_{445} strong expression in the hippocampus, suggests that histamine participation in learning and memory processes would be mediated by the latter receptor. On the other hand, the 413 aa isoform in the rat is predominantly expressed at the dorsal raphe nucleus and in the locus coeruleus, suggesting that this isoform is responsible for serotonin and noradrenalin release inhibition, whereas isoforms hH_3R_{445} strong expression in granular cells and hH_3R_{397} in Purkinje cells of the rat would indicate differential participation of both these isoforms in cerebellum motor functions regulation.

In summary, available information suggests that in humans and in the rat, two isoforms with a lower number of amino acids in region i3 (hH_3R_{365} and hH_3R_{413}, respectively) might preferably express in histaminergic neurons and, consequently, be responsible for the triggering frequency modulation and for the synthesis and release of histamine itself. Conversely, the 445 aa isoform function appears to be more generalized and its effects would include modulation of the cortex → basal ganglia → thalamus → cortex motor circuit, as well as of affective behaviors through regulation of the limbic system.

Of the 20 hH_3R isoforms identified to date, 12 might be non-functional, since they lack critical regions for agonist binding and/or signaling. However, in the rat, three 497, 465 and 449 aa isoforms (rH_3R_D, rH_3R_E and rH_3R_F), which lack the TM7 region (necessary for agonist binding)[56-59] and which also possess a 105 aa extracellular carboxyl extreme, without homology with the carboxyl domain of the 7-TM variants (rH_3R_A, rH_3R_B and rH_3R_C, with 445, 413 and 397 aa, respectively), significantly reduce cell membrane expression of the 445 aa isoform (rH_3R_A) when co-expressed in COS-7 cells[60]. Thus, one possibility is that co-expression of non-functional hH_3R isoforms regulates the expression and functionality of functional isoforms in the human CNS.

Conclusions

The control of the release of histamine itself and other neurotransmitters, particularly acetylcholine, dopamine,

noradrenalin and serotonin, has led to consider the H_3R an important target for pharmacological approach to neurological disorders such as schizophrenia, cognitive disorders, migraine, Alzheimer and Parkinson diseases, Gilles de la Tourette syndrome and hyperactivity disorder with attention deficit[9,26,61-69]. The presence of several hH_3R functional isoforms, with heterogeneity in their pharmacological and signaling characteristics, as well as with differential expression patterns on different brain areas, suggests a fine regulation of the CNS function by the histaminegic system. Further understanding of the pharmacological and functional behavior of hH_3R isoforms will also enable the design of selective ligands for them and this way more specifically act on CNS alterations where the histaminergic system has been involved.

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Conflict of interests

The authors declare not having any conflicts of interests.

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