Biomedical & Pharmacology Journal, September 2025. Vol. **18**(3), p. 1849-1862

Review on H3 Receptor Modulators: Future Pioneering approaches in Dementia Treatment

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https://dx.doi.org/10.13005/bpj/3219

(Received: 24 February 2025; accepted: 08 July 2025)

Current treatment options for Alzheimer's disease target neurotransmitters following the disease onset, and they offer limited efficacy without slowing down the disease progression. There has been an elevating concern in recent years targeting Histamine H3 receptor in treating cognitive disorders, including dementia. Preclinical studies have shown that antagonists of H3 receptor or inverse agonists enhances the cognitive function in animal models with dementia by increasing the release of neurotransmitters associated with learning and memory. The primary aim of this study is to explore the pathophysiological mechanisms underlying Alzheimer's disease (AD), with a specific focus on the role of the histamine H3 receptor (H3R) and its modulators. This review employed a systematic literature search across databases including PubMed, Scopus, Google Scholar, and ClinicalTrials.gov, selecting peer-reviewed studies published between 2000 and 2024. Results of the study illustrate the complex landscape of research on H3 receptor modulators in dementia, highlighting both promising findings and ongoing challenges in translating preclinical discoveries into effective clinical interventions. Knowing the Histamine H3 receptors role in dementia and developing novel pharmacological interventions targeting these receptors represent a promising avenue for future research leading to new treatments development to this devastating condition.

Keywords: Dementia; Findings; Histamine; Modulators; Receptors; Research.

Alzheimer is a degenerative & incapacitating neuro condition marked by gradual Cognitive abilities deterioration, specifically impairment of memory & diminished reasoning. This is the primary cause of cognitive decline in elderly individuals, affecting many people globally. The disease, named after the German neurologist Alois Alzheimer, who initially documented the condition in 1906,[1] primarily impacts the brain by causing the buildup of atypical protein deposits like beta-amyloid plaques and tau tangles and the demise of nerve cells.These atypical formations interfere with the regular transmission of signals between neurons, leading to the progressive decline of cognitive functions like memory, language, problem-solving, and daily activities. [2]

The precise etiology of Alzheimer's disease remains elusive; however, advancing age, genetic predisposition, and lifestyle factors are considered potential determinants in its

pathogenesis. The disease exhibits individual variability in its progression, typically commencing with mild symptoms that gradually deteriorate over time. [2] Alzheimer's disease not only impacts the individuals who are diagnosed but also imposes a considerable emotional and physical strain on their families and caregivers. Despite thorough investigations, there is presently no remedy for Alzheimer's disease. The treatment options have the goal of mitigating symptoms and improving the quality of life for individuals who are impacted. Current scientific endeavors are concentrated on comprehending the fundamental mechanisms of the disease, creating early diagnostic assays, and investigating potential therapeutic interventions.

The primary aim of this study is to explore the pathophysiological mechanisms underlying Alzheimer's disease (AD), with a specific focus on the role of the histamine H3 receptor (H3R) and its modulators. This study aims to examine how H3R modulation influences cognitive decline and neurodegeneration in AD, evaluate its potential as a therapeutic target, and investigate the implications of H3R modulators in the treatment of Alzheimer's disease. Additionally, the study will aim to analyze the relationship between H3 receptor activity and neurotransmitter systems involved in AD, providing insights into novel therapeutic strategies for improving cognitive function and slowing disease progression.

Drug targets for the treatment of dementia

Ongoing research into drug targets for Alzheimers is advancing, with an exploration of the multiple potential targets. It is crucial to acknowledge that drug development is an intricate procedure, and numerous potential treatments undergo a thorough examination in preclinical and clinical trials prior to being released in the market. Scientists are constantly investigating new methods, and our knowledge of the underlying causes of Alzheimer's disease is developing. The primary drug targets that are being studied for Alzheimer's disease are summarized below:

Beta-Amyloid Plaques

Beta-amyloid is a protein that creates deposits in people brains who have Alzheimer's disorder. Scientists have been investigating medications that specifically target beta-amyloid, with the goal of decreasing its production or improving its removal. Nevertheless, clinical trials focused on beta-amyloid have yielded inconclusive outcomes, and the beta amyolid importance in this disease continues to be actively studied.

Post-translational modification of Amyloid Precursor Protein -APP involves cleavage at á- or â-side enzymes, and processing of C-terminal fragment produced by gamma secretase. If cleavage is from the á-secretase product, it results in a non-toxic protein fragment (p3), but the products of the cleavages by the Beta site cleavage enzyme – BACE & the Gamma secretase yield 38-43 Amino acid flibrillogenic Amyloid-beta protein (Aâ), though $Aâ_{42}$ which is the very much prone to deposition identified in the Core neuritic plaques.[3] To reduce Aâ production, efforts have been made to target drugs that can activate alpha secretase, [4] or inhibit beta and gamma secretase, [5] Degradation of toxic form of Aâ is also a target for dementia management as Aâ degradation enzymes are low in human [6] & animal [7] AD models, and the endogenous pathways to achieve this include neutral endopeptidase (neprilysin),[8] metalloproteinase, endothelin-converting enzyme,angiotensin-converting enzyme.

Studies have shown that constitutive monomer form of Aâ or fibrillar network form aggregated in plaques is not the synaptotoxic form,[9] but rather the oligomerization of monomeric Aâ into dimer, trimer & other higher molecular mass combinations at aggregation stage. Thus, oligomeric inhibition is a top target for the prevention of AD. Some agents that are at different stages of clinical trial for the prevention of oligomerization Aâ include grape-derived polyphenols, [10] curcumin & Omega-3 fatty acids.[11]

Tau Protein

Intracellular Neuro Fibrillay Tangle, which is a condensed from of cycloskeletal structure consisting hyper phosphorylated helical paired filaments of microtubule associated with Protein Tau, is the second pathological marker of AD. While Tau phosphorylation is important for its functioning, the hyper phosphorylated Tau does no longer binds the microtubule but rather aggregate into paired helical filaments,[12] ultimately leading to microtubule instability and disruption of axonal transport. Various kinases, including Glycogen synthase kinase 3 beta (GSK-3â) & Cyclin dependant kinase – 5, that is involved in tau hyper phosphorylation have been identified

and are of therapeutic target. Agents like lithium and valproate inhibit GSK-3â to stabilize tau. Protein phosphatases, which dephosphorylate tau, are also important target for the inhibition of hyperphosphorylation.[13]

Cholinergic System

Inhibition of cholinergic function leads to attention deficit, while facilitation of cholinergic transmission improves it. [14] The major role of cholinergic system on learning proces, and memory [15] have been established, as endogenous acetylcholine modulates the acquisition, encoding, [16] consolidation,reconsolidation,[17] extinction,[18] & memory retrieval.[19] In fact, memory loss in AD patients is associated with cholinergic neurons degeneration from nucleus basalis of Meynert.[20] There is evidence showing cholinergic system disruption impairs memory, attention, and learning. [21] Some examples of drugs that target the cholinergic system are acetylcholinesterase inhibitors and neuronal nicotinic receptors' agonists. [22]

Serotonergic modulation

The expression of serotonin receptors in the brain areas important for memory & learning, and their decline in AD and dementia have been well-established. [23] Moreover, the beneficial effect of selective agonists and antagonists of serotonin receptors on cognition in animal [24] & human [25] models have been reported.

Inflammation

Neuroinflammation is thought in contribution to advancement of Alzheimer's Disease. Researchers are currently studying anti-inflammatory medications and substances that specifically target inflammatory pathways as potential treatments. Some drugs involved in the regulation of inflammation that are under different clinical trial phases on AD are Masitinib, NE3107, [26]Semaglutide, AL002, [27] Bacillus Calmette-Guerin, [28] Baricitinib,[29] Canakinumab [30], Daratumumab [31], Lenalidomide [32], Montelukast [33], Pepinemab [34], Proleukin [35], Rapamycin ,[36] Sargramostim, [37] Senicapoc, [38] TB006,[39] Tdap vaccine, [40] Valacyclovir, [41] XPro1595, [42] CpG1018, [43] Emtricitabine, [44] IBC-Ab002,[45] Salsalate,[46] VT301.[47]

Neuroprotective Factors

Certain studies focus on investigating factors that enhance the resilience of nerve cells, shielding them from harm and boosting their longevity. This encompasses neurotrophic factors and other molecules that have the potential to augment neuronal resilience, enhancing synaptic plasticity, or produce neuroprotective effects. Some of the drugs at different phases of clinical trial include AGB101,[48] Blarcamesine,[49] Fosgonimeton, Simufilam, [50]Tertomotide, [51] AL001, [52] Bryostatin1,[53] CY6463, [54] Dalzanemdor, [55] Edonerpic, [56] Elayta, [57] EX039, [58]ExPlas,[59] MW150,[60] Neflamapimod ,[61] and Centella asiatica. [62]

Neurogenesis

Agents that promote neurogenesis are among those that are in the treatment pipeline for the treatment of AD. An example is allopregnanolone, that is an allosteric modulator of inhibitory Gamma aminobutyric acid-A receptors, which reduced deposition of amyloid and enhanced memory and learning. [63] Another example is sovateltide, an Endothein -B receptor antagonist that helps in promoting differentiating neuronal progenitors for production of mature neuronal cells which exhibits anti-apoptotic, antioxidant, & enhancement of functional properties of mitochondria . [64]

Genetic factor

Persons carrying apolipoprotein E 4 are at high risk of developing AD at earlier age, as it leads to increased Aâ deposition in the brain by regulating the passage of Aâ from the blood to the brain. Some drugs target apolipoprotein E 4 gene carrier (*APOE4*), being a very influential risk factor after the age of an individual & the most vital genetic factor for the AD development. This protein makes strong interaction with Aâ, thereby reducing the amyloid brain accumulation age & elevating the total Aâ burden in gene carriers. [65] Furthermore, *APOE4* exacerbates Tau neuro-fibrillary tangle-related blood brain barrier disruption neurofibrillary tangle-dusruption, neurodegeneration, microglial responses, astroglial activity and neuroinflammation. [66] Some therapies to targeting this marker are hydroxypropyl-beta-cyclodextrin, [67] LX 1001, and obicetrapib. [68]

Oxidative stress

Evidence have shown that enhancement of antioxidant status and attenuation of oxidative stress can reduce, prevent or treat AD, as the food rich polyphenols, antioxidants & poly unsaturated fatty acids reduce AD risk. [69] Drugs

like hydralazine, [70] edaravone, [71] among others, are at various clinical trials stages for management of AD.

Others

There are other mediators and pathways that are targeted for drug development on the management of AD. Some of these are drugs that regulate vascular factors (telmisartan, perindopril), circadian rhythm (piromelatine), [72] and epigenetics (lamivudine). [73]

Lifestyle and Supportive Interventions

Non-pharmacological interventions are essential for effectively managing the symptoms of Alzheimer's disease. These factors encompass cognitive stimulation, physical activity, and a nutritious diet. Establishing a nurturing and organized setting can additionally improve the general welfare of individuals who have AD.

Clinical trials and Research on Histamine-receptor in AD treatment

Ongoing research is being conducted to formulate novel treatments and therapies for Alzheimer's disease. Clinical trials provide the opportunity to access experimental medications or interventions that are currently undergoing testing to determine their efficacy.

Alzheimer's research is constantly evolving, with continuous endeavors to discover novel therapeutic targets and create more efficient interventions. It is recommended that individuals suffering from Alzheimer's, their families and caregivers, remain updated on the most recent research discoveries and treatment choices by consulting with healthcare professionals and reliable sources.

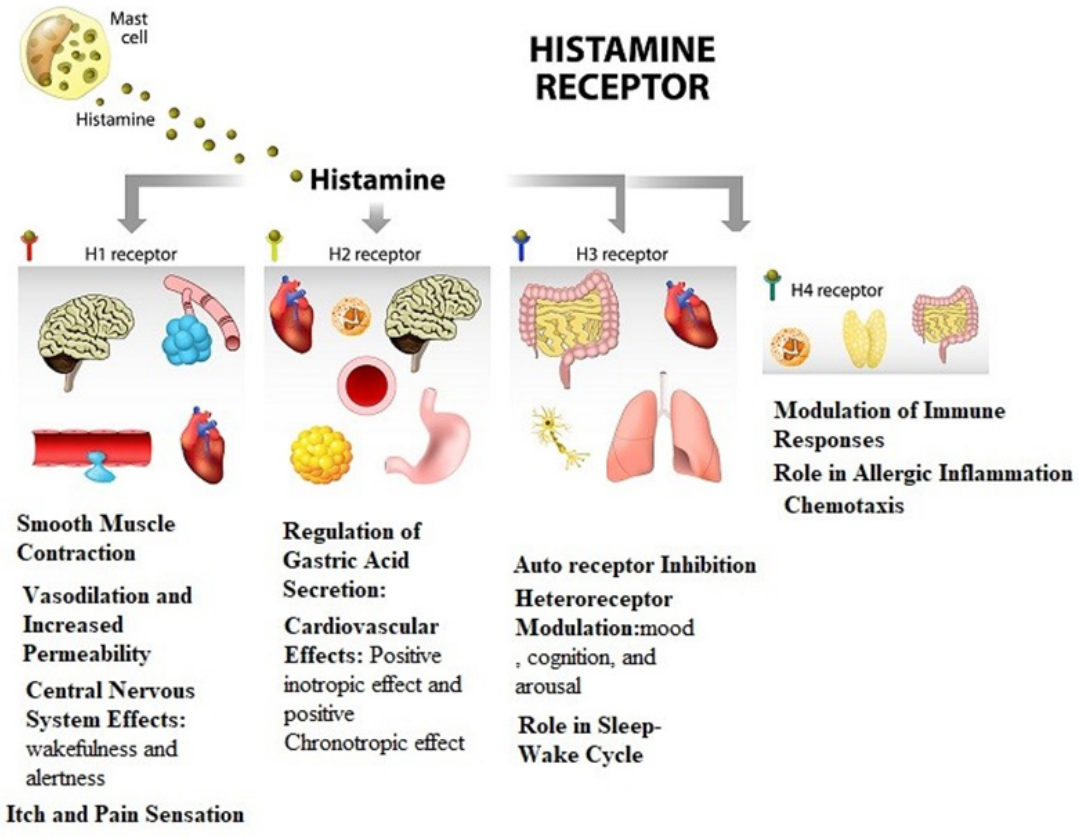

Fig. 1. Overview of Histamine regulation

Table 1. Characteristics of Histamine Receptors

S. No	Ty2pe	Location Central	Peripheral	Function	Binding Affinity to Histamine (pKi)	Signalling Pathway (Figure 2)	Ref
1	H1R	Forebrain, cerebral cortex,Hippocampus, Thalamus	Heart and smooth muscles	Decreasing BP, inflammatory response, and increased wakefulness	4.2	Phospholipase C (PLC)	84
2	H2R	SubstantiaNigra, raphe nuclei, Hippocampus and Basal ganglia	Intestine smooth muscles, heart, and lungs	Regulation of hormone release, fluid balance, excitation, relaxation of airway smooth muscles, blood pressure regulation and gastric acid regulation	4.3	Protein kinase C activation(PKC)	85
3	H3R	Cerebral cortex, basalganglia, hypothalamus	Lung, CVS, intestine	Histamine release regulation and stimulation	8.0	Inhibition of PKA, activation of Phospholipase 2, MAPK	86
4	H4R	Cerebellum & hippocampus	Hematopoietic Cells	Modulation of Immune system	7.8	PKA Inhibition, Phospholipase C & MAPK activation.	87

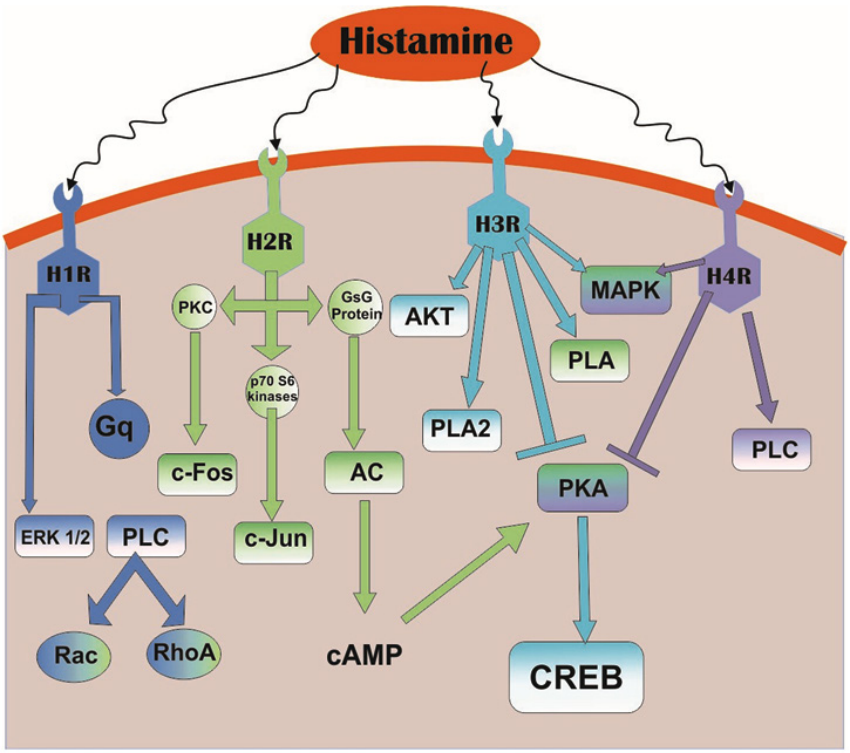

Fig. 2. Histamine receptors - Signalling pathways

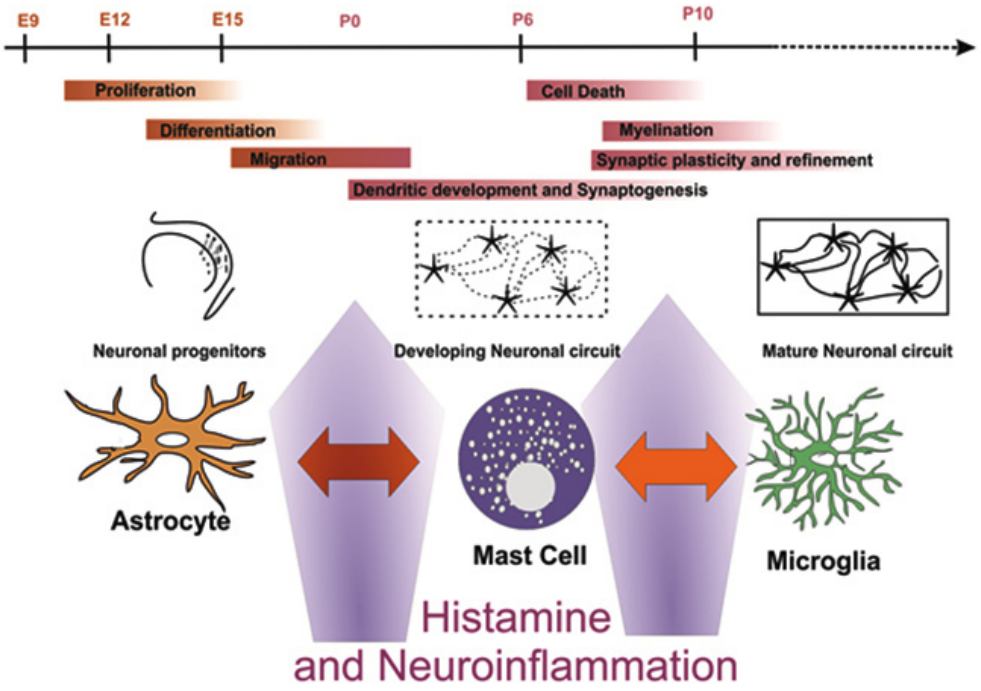

Fig. 3. Role of histamine in neuronal development

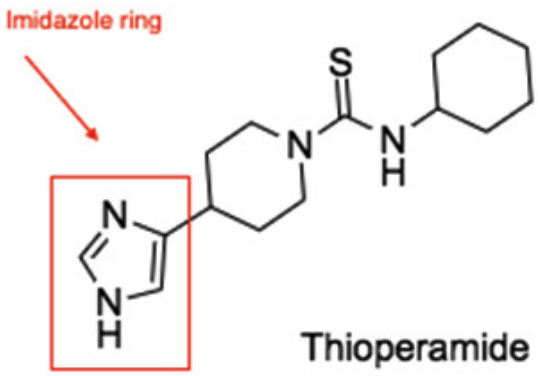

Fig. 4. Structure of Thioperamide

Histamine

Histamine is a neurotransmitter that performs various physiological functions in the body through four receptor subunits, including G-protein coupled H1, H2, H3, & H4, and various agonists and antagonists were developed for these receptors.[74] Allergic indications like asthma, rhinitis, conjunctivitis, & atopic dermatitis are treated with H1 histamine receptor antagonists. [75] Activation of H2 receptors stimulates the gastric secretion, and H1 & H2 receptors mediate the opposing pharmacological and physiological effects on lungs and heart. [76] H3 histamine receptor is a presynaptic autoreceptor that inhibits the production & release of histamine in histaminergic neurons,[77] while the H4-receptor is expressed in the immune cells. Evidence has shown that both H3 and H4 have homology and some H3 agonists & antagonists equally bind to H4 receptor. [78]

Arecent nationwide cohort study in Taiwan showed that the use of H1 receptor antagonist is linked with increased dementia risk. [79]

H3 histamine receptor is encoded on chromosome 20 and it is displayed in many regions of brain like Cerebral cortex, CNS basal ganglia, & hypothalamus, all of which play some important roles in cognition. [80] It binds to Gi protein to negatively control the intracellular second messenger cAMP. [81] Histamine is known to downregulate the acetylcholine-induced calcium signaling of the muscarinic receptor via H3 histamine receptor-mediated mechanisms. [82] It is also known that H3 receptor antagonists can stimulate histamine, dopamine, acetylcholine & norepinephrine, all of which are participated in some specific cognition aspects, making H3 receptor antagonists important drug targets to improve cognition in dementia patients.

H3 receptor inverse agonists can increase histaminergic neuron activity by inhibiting the H3-receptor mediated suppression of histamine release in brain, making them a target for AD treatment drug development.

Although there are current studies investigating the involvement of histamine in neurodegenerative diseases, such as dementia, the connection between the two is intricate, and our comprehension is still incomplete. Below are several key factors concerning the potential role of histamine in dementia progression role. [83]

Role of the Histamnie in the pathogenesis of dementia

Histamine interacts with histamine receptors, specifically receptors 1, 2, and 3. Cognitive deficits occur when histamine is unable to bind to receptors. The H3 Rreduces histamine release in brain, resulting Alzheimer's disease. Inverse agonists of H3R are crucial in counteracting the effects of histamine-induced Alzheimer's disease. [88-89]

Antagonists of Histamine 3 receptors stimulate the production of histamine, ACh, and other neurotransmitters, thereby enhancing cognitive function. Histamine plays a role in both short-term and long-term cognitive processes. [90] Recent studies indicate that the deterioration of histamine neurons is the causative factor

in Alzhemer's development. The presence of histamine in the brain improves cognitive function and memory, although the specific mechanism by which it does so remains unclear. [91] The histaminergic neuron system in the brain regulates various roles i.e., homeostasis, learning arousal & memory, and circadian rhythms. Furthermore, certain studies explained that histamine plays a part in regulating specific behavioral tasks, although the underlying mechanism remains unclear. [92] To treat Alzheimer's disease (AD), various pre-clinical methods have been developed to specifically target H3 receptors.[93]

The development of AD is attributed to the induction of neurotoxicity by beta-amyloid 1-42. However, this neurotoxicity can be mitigated by histamine acting on histamine receptors (H2 and H3). [94] Using H2 receptor agonists leads to a gradual reduction in AD (Anthony et al. 2000). Using H2 receptor agonists leads to a gradual reduction in AD (Anthony et al. 2000). HIR-KO mice exhibit cognitive symptoms because of alterations in brain levels of AChE and dopamine. [95]The involvement of Histamine 1 & 2 receptors in cognitive function is substantiated by the presence of cognitive deficits resulting from null mutations in the genes encoding these receptors. Both H1 and H2 are excitatory neurotransmitters, whereas H3 functions differently as an inhibitory neurotransmitter and acts as an auto heteroreceptor. Interactions between histaminergic, peptidergoc & aminergic systems can be able to regulate homeostatic functions like Sleep wake cycles, cognition & synaptic plasticity. [96] The compound GSK189254, a high-affinity histamine 3 receptor antagonist, has shown therapeutic potential for Alzheimer's disease in both rats and humans [97]. Histamine is involved in cognitive processes, but the interaction between histamine and histamine 3 receptors lowers the cholinergic function in hippocampus and frontal cortex. [98] The H3 antagonists (ABT-239) enhanced the symptoms of Alzheimer's by stimulating the biochemical signaling and inducing tau hyperphosphorylation. (Figure 3) [99]

Histamine receptors are involved in regulating the functional activity of dendritic cells subsets. The H2R antagonist characterizes the specific mechanisms of histamine induced decrease of CD1a (+) DCs, IL6 & IL10 increased production, upregulation of chemokines, expression of C5aR1 through the CD1a (") & DC subset, and increased migration of activated DC subsets, which is stimulated by secretion of MMP-9 & MMP-12 enzymes. [100] SOCE or store-operated calcium entry, is the main mechanism by which DCs (dendritic cells) allow Ca2+ ions to enter.

DCs that have been primed with histamine can initiate the Th2 immune response by interacting with several types of histamine receptors. Dendritic cells (DCs) are activated by histamine, which trigger the release of calcium ions (Ca2+) from their intracellular reservoirs. Histamine elevates IL-10 levels while decreasing the IL-12p70 levels that are produced by DCs. Pretreating dendritic cells (DCs) with H1R antagonists, SOC blockers, and H4R antagonists can prevent the histamine-induced Th2 polarisation of T-helper cells in the mixed responses of lymphocytes. Recent research indicates that SOCE (Store-Operated Calcium Entry) is crucial in the Th(2) response and histamine-induced maturation of dendritic cells through activation of both H1R and H4R. [101] Research has demonstrated that young individuals who produce elevated levels of IL-2 and IFN-ã possess a specific type of T-cell memory called beta (1-42)-specific Th1-type T-cell memory. There is evidence indicating that as individuals age, there is a decline in the production of IFN-ã and IL-2, while there is a noticeable increase in the release of regulatory IL-10 by CD4(+) T-cells. However, despite of the absence of an effector cytokine, individuals with AD can still generate IL-10. [102] The proinflammatory cytokine IL-32 can activate nuclear factor êB & p38 mitingen activated protein kinase (p38MAPK) pathways. IL-32 can induce histamine synthesis in human derived core blood mast cells (HDCBMCs; Figure 1). Therefore, it can be demonstrated that IL-32 is specific to a particular species and functions in fully developed human mast cells (LAD 2 cells). [103] Research has demonstrated that IL-32 plays role in controlling neuro inflammatory responses in various neuro diseases, including Alzheimer's disease. [104]

Recently developed drugs for the treatment of dementia by blocking H3 receptors

Thioperamide

Thioperamide is a highly potent and specific antagonist of imidazole. It was primarily developed to improve wakefulness and address

issues related to learning and memory. According to recent research, thioperamide, despite its hepatotoxicity, has been found to have a significant impact on patients with circadian rhythm disorders & Parkinson's disorder. [105] (Figure 4)

Pitolisant

Pitolisant is the potent H3 receptor antagonist/inverse agonist that has been approved by regulatory agencies in the United States and Europe. Its high oral bioavailability allows easy access to the brain. It undergoes metabolism by the enzyme CYP4A in the gastrointestinal tract. It is employed in managing narcolepsy to sustain wakefulness during the daytime. Headache, anxiety, and QT prolongation have been documented as adverse effects in clinical trials. [106] Wakix is a proprietary name for a product that has been commercially available since March 2016. The dosage is available in tablets of 4.5 mg and 18 mg.

Neuropharmacology has a lot of potential due to the fact that H3 receptor modulators are being used to treat dementia after being experimentally developed. Investigating these modulators has yielded valuable understandings of the intricate mechanisms that underlie dementia and has unveiled fresh prospects for therapeutic interventions. The bench-to-bedside approach prioritizes the smooth conversion of scientific findings into tangible implementations for patient treatment.

The combined endeavors of researchers, clinicians, and pharmaceutical developers are instrumental in creating groundbreaking solutions that could revolutionize dementia treatment in the future. As research and clinical trials progress, our understanding of H3 receptor modulators will improve, leading to a better understanding of their role in the comprehensive care and management of dementia patients.

Future Prospective

While H3 receptor modulators seem to be promising potential therapeutic agents for dementia, further research and development efforts are needed to realize their full clinical potential and impact on patient outcomes. Collaboration between academia, industry, regulatory agencies, and patient advocacy groups will be essential in advancing this field and addressing the growing burden of dementia worldwide.

CONCLUSION

H3 receptor modulators represent a promising frontier in dementia treatment, offering potential therapeutic benefits by modulating histaminergic neurotransmission. Their role in cognitive enhancement, neuroprotection, and synaptic plasticity underscores their significance in addressing dementia-related pathophysiology. Preclinical and clinical studies highlight their efficacy, yet challenges such as selectivity, safety, and long-term effects remain to be addressed. Future research should focus on optimizing drug design, exploring combination therapies, and conducting extensive clinical trials to ensure translational success. With continued advancements, H3 receptor modulators may emerge as pivotal agents in the fight against dementia.

ACKNOWLEDGMENT

All authors are thankful to Management of Sandip University, Nasik, for providing facilities.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not applicable.

Author's contribution

Nagaraju Bandaru. and Mohiyuddin Ikramuddin Shaikh: Contributed to

conceptualization and methodology, Nagaraju Bandaru, Wagh Sakshi Krishna and Krunal bhai Rameshbhai: Performed the literature research, analyzed the data and drafted the manuscript, Makarand Suresh Gambhire: Critically revised the work, All the authors have read and agreed to the published version of the manuscript.

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