Histamine-4 Receptor: Emerging Target for the Treatment of Neurological Diseases

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Abstract A major challenge in the field of the biogenic amine histamine is the search for new-generation histamine receptor specific drugs. Daniel Bovet and Sir James Black received their Nobel Prizes for Medicine for their work on histamine-1 receptor (H_1R) and H_2R antagonists to treat allergies and gastrointestinal disorders. The first H_3R-targeting drug to reach the market was approved for the treatment of the neurological disorder narcolepsy in 2018. The antagonists for the most recently identified histamine receptor, H_4R, are currently under clinical evaluation for their potential therapeutic effects on inflammatory diseases such as atopic dermatitis and pruritus. In this chapter, we propose that H_4R antagonists are endowed with prominent anti-inflammatory and immune effects, including in the brain. To substantiate this proposition, we combine data from transcriptional analyses of postmortem human neurodegenerative disease brain samples, human genome-wide association studies (GWAS), and translational animal model studies. The results prompt us to suggest the potential involvement of the H_4R in various neurodegenerative diseases

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and how manipulating the H_4R may create new therapeutic opportunities in central nervous system diseases.

Keywords Histamine 4 receptor · Microglia · Parkinson's disease and amyotrophic lateral sclerosis

1 Introduction

Histamine and histamine receptors are known for their involvement in allergic and inflammatory reactions in the periphery (Dale and Laidlaw 1910). Dr. Daniel Bovet won the 1957 Nobel Prize for Physiology or Medicine for his discovery of a histamine 1 receptor (H1R) antagonist which has been widely used in allergy medication (Leurs et al. 2011; Tiligada and Ennis 2020). Sir James Black was awarded the Nobel Prize for Medicine in 1988 for the development of a histamine 2 receptor (H_2R) antagonist that has been used for the treatment of stomach ulcers (Leurs et al. 2011; Tiligada and Ennis 2020).

A neurotransmitter function for histamine became apparent from the pharmacological identification of the H_3R (Arrang et al. 1983) and the localization of the exclusive site of neuronal histamine production in the tuberomammillary nucleus (Watanabe et al. 1983; Panula et al. 1984). H_3R is an auto- and heteroreceptor that regulates multiple physiological functions including release of neurotransmission, not only the release of histamine but also of other biogenic amines (acetylcholine, dopamine, 5-hydroxytryptamine, and noradrenaline) (Passani and Blandina 2011; Panula et al. 2015). Its functions/features highlighted the therapeutic potential of H_3R ligands for the treatment of neurodegenerative disease and sleep disorders. The successful development of the H_3R antagonist/inverse agonist pitolisant for the treatment of excessive sleepiness in narcolepsy encouraged a search for clinical targets of the most recently discovered histamine receptor H_4R.

Different from the other histamine receptors, the H_4R has been discovered by a genomic approach and was described almost simultaneously by six laboratories (Nakamura et al. 2000; Oda et al. 2000; Liu et al. 2001; Zhu et al. 2001; Morse et al. 2001; Nguyen et al. 2001). H_4R antagonists show positive effects in several preclinical models of human diseases including asthma, dermatitis, collagen-induced arthritis, colitis, and histamine-induced pruritus (Thurmond et al. 2008; Mehta et al. 2020). Applications of these antagonists are, therefore, currently advancing into clinical trials such as for atopic dermatitis and pruritus (Thurmond et al. 2008, 2017; Leurs et al. 2011). However, there are also potential applications of H_4R for the treatment of central nervous system diseases. This review intends to give an overview of the emerging role for the H_4R in the brain and suggests therapeutic potentials of H_4R ligands for the treatment of neurodegenerative diseases.

1.1 Neurobiology of Histamine

Histaminergic neurons are located solely in the posterior hypothalamic tuberomammillary nucleus and innervate a large number of brain areas, such as the cerebral cortex, hippocampus, amygdala, thalamus, hypothalamus, and spinal cord (Panula and Nuutinen 2013; Shan et al. 2013). In the tuberomammillary nucleus, neuronal histamine is synthesized from histidine through the key enzyme histidine decarboxylase (HDC) (Haas et al. 2008). Brain histamine is mainly reduced to its inactive form tele-methylhistamine (t-MeHA) by histamine N-methyltransferase (HMT). The alternative inactivation, oxidation, also takes place in the brain by diamino-oxidase (DAO). Histamine exerts its functions via the four types of G protein-coupled histamine receptors ($H_{1\text{-}4}R$) (Panula et al. 2015). In general, these receptors are involved in basic physiological functions including sleep–wake cycle modulations, energy metabolism, endocrine homeostasis, sensory and motor functions, cognition, addiction, pain, learning, and memory (Haas et al. 2008). As several authoritative reviews have discussed the pharmacology, signal pathways, and physiological functions of histamine receptors ($H_{1\text{-}4}R$) (Passani and Blandina 2011; Panula et al. 2015; Yoshikawa et al. 2020), we here focus on the therapeutic potentials of H_3R and H_4R.

H_3R was first characterized as an auto-receptor regulating histamine synthesis in the tuberomammillary nucleus and histamine release from the cerebral cortex, striatum, and hippocampus in the rat (Arrang et al. 1985a, b, 1988b). In the human cerebral cortex, H_3R inhibits histamine release (Arrang et al. 1988a). Deficiency of the histamine-stimulated presynaptic auto-receptor in H_3R knockout mice demonstrated increased concentrations of histamine and tele-methylhistamine (t-MeHA) in the hypothalamus and thalamus (Takahashi et al. 2002). H_3R knockout mice showed increased anxiety and improvements in spatial learning and memory in the Barnes maze (Rizk et al. 2004) and pronounced sleep fragmentation (Takahashi et al. 2002; Gondard et al. 2013). It should be noted that H_3R knockout animals lack both auto and heteroreceptors; therefore, the phenotypical changes may also be related to other neurotransmitter systems. Several clinical trials have been conducted or are ongoing to explore the positive therapeutic effects of H_3R antagonists, including the treatment of Alzheimer's disease, schizophrenia, and narcolepsy. Unfortunately not much positive cognitive effects have been reported in humans. To date, one H_3R antagonist/inverse agonist, pitolisant, successfully reached both the US and the European markets for the treatment of narcolepsy type 1.

Postmortem human brain findings are an invaluable starting point for the development and validation of animal models for psychiatric disorders and neurological diseases. Pitolisant is a good example of how postmortem findings increase our insight and direct the search for validated translational animal models for preclinical tests. Narcolepsy type 1 is a rare and often disabling disorder that is characterized by excessive daytime sleepiness, short-onset rapid eye movement sleep, and cataplexy (sudden loss of muscle tone), accompanied by hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep (Bassetti et al. 2019). Although narcolepsy

has been recognized by clinicians nearly 150 years ago, a breakthrough was the finding in postmortem studies on narcoleptic patients with cataplexy that the number of hypocretin (orexin)-producing neurons has decreased by 90% (Peyron et al. 2000; Thannickal et al. 2000). Earlier, a dog model, later linked to a mutation in the hypocretin receptor 2 gene, was generally accepted as narcoleptic animal model, because it exhibited strong cataplexy and sleep impairment similar to the symptoms of patients with narcolepsy (Nishino et al. 1991). Based on the postmortem findings, a number of rodent narcolepsy models have been developed, including the hypocretin knockout mouse (reviewed in (Shan et al. 2015a)). Hypocretin peptides are produced exclusively by a cluster of neurons in the medial and lateral hypothalamus, which are adjacent to and functionally interact with histaminergic neurons (Shan et al. 2015b). Histaminergic neurons promote cortical activation and wakefulness (Anaclet et al. 2009; Yu et al. 2015). Increased histamine signaling might counteract a tendency toward hypersomnia and help to maintain consciousness during cataplexy by preventing full transitions into rapid eye movement sleep. In line with this hypothesis, H_3R antagonists elevate the cortical level of t-MeHA in hypocretin knockout mice and significantly improve the main symptoms of narcolepsy, including excessive daytime sleepiness and short rapid eye movement sleep latency at sleep onset (Lin et al. 2008; Guo et al. 2009). Two follow-up randomized, double-blind placebo-controlled trials confirmed the efficacy and safety of pitolisant in narcolepsy types 1 and 2 (Dauvilliers et al. 2013; Szakacs et al. 2017). In contrast with other treatments such as amphetamines and sodium oxybate (Bassetti et al. 2019), the use of pitolisant is not associated with addictive features in preclinical rodent and primate models (Uguen et al. 2013; Brabant et al. 2016; Huyts et al. 2019). Based on these experimental data, both the European Medicines Agency and the United States Food and Drug Administration approved pitolisant for the treatment of excessive sleepiness in narcolepsy (Kollb-Sielecka et al. 2017). We will therefore follow the same approach, from postmortem human brain findings to validated animal models, to search for potential therapeutic targets of H_4R manipulation.

1.2 Neurobiology of the H_4R

Based on the phenotypes of its knockout mice, H_4R modulates a series of distinct functions, including locomotor activity, anxiety, nociception, and feeding behavior, without an influence on working and recognition memory (Sanna et al. 2017). However, the phenotype of a genetically modified animal is not sufficient to determine the role of the receptor in different conditions. Compensatory mechanisms can be always present and contribute to the phenotype observed. Pharmacological modulation is therefore an important addition to understand the functional aspects of the receptor. Because of the controversy around the specificity of H_4R receptor antibodies (Beermann et al. 2012; Schneider and Seifert 2016), we here selectively focus on mRNA expression data and data from using specific H_4R ligands. Reverse

transcription polymerase chain reaction (RT-PCR) revealed H_4R mRNA expression in many human and rat brain regions, including the amygdala, cerebellum, corpus callosum, frontal cortex, and thalamus (Strakhova et al. 2009). In addition, H_4R-mRNA is expressed in a range of sensory signaling pathways, such as in the vestibular nucleus neurons in rats (Desmadryl et al. 2012), and in the thalamus and in the spinal cord of both rat and human (Strakhova et al. 2009). Of note, H_4R antagonists have a pronounced inhibitory effect on vestibular neuronal activity (Desmadryl et al. 2012; Petremann et al. 2020). The involvement of H_4R in both acute (Galeotti et al. 2013) and persistent inflammatory pain (Hsieh et al. 2010) made this receptor a promising target for neuropathic pain treatment (Sanna et al. 2015, 2020). However, the exact role of the H_4R in neuropathic pain is thus far unclear (reviewed in (Obara et al. 2020)).

H_4R mRNA is selectively expressed in the periphery in cells of hematopoietic origin including dendritic cells, mast cells, eosinophils, monocytes, basophils, and T cells known to be involved in inflammatory and immune responses (Nakamura et al. 2000; Oda et al. 2000; Liu et al. 2001; Zhu et al. 2001; Morse et al. 2001; Nguyen et al. 2001). Moreover, H_4R-mRNA is expressed in rat brain endothelial cells where this receptor is important for the regulation of blood-brain barrier (BBB) permeability (Karlstedt et al. 2013). A number of neurological diseases show an impairment of BBB integrity, causing the interaction of different neural and immune cells (Profaci et al. 2020). Systemic and chronic administration of the specific H_4R antagonist JNJ7777120 reduced ischemic neuronal damage and improved sensorimotor deficits in an ischemia model where the BBB was severely damaged. These changes were accompanied by a reduction in the number of ionized calcium-binding adaptor molecule-1 (Iba-1)-positive microglial cells in the rat brain (Dettori et al. 2018). Interestingly, microglia largely originate from the hematopoietic system (Eglitis and Mezey 1997; Bian et al. 2020). H_4R-mRNA has been identified in immortalized microglia N9 cells, in cortical slice cultures and explants (Ferreira et al. 2012), and rodent primary microglial cultures (Dong et al. 2014). Single-cell RNA-sequencing of human surgical-derived cortical microglia showed that H_1R-, H_2R-, and H_4R-mRNAs are present at comparable levels (Masuda et al. 2019). It should be noted that the H_4R has an nM affinity for histamine that is similar to that of H_3R and higher than of the H_1R and H_2R which are in the μM range (Panula et al. 2015). H_4R plays a key role in microglial activation in vivo (Ferreira et al. 2012; Dong et al. 2014; Zhang et al. 2020). The results regarding the effects of H_4R on microglia in in vitro and in vivo studies have been contradictory. Lipopolysaccharide (LPS)-induced pro-inflammatory cytokine interleukin-1β (IL-1β) release from both the N9 microglia cell line and hippocampal organotypic slice cultures were inhibited by the H_4R agonist 4-methylhistamine (Ferreira et al. 2012). In contrast, other reports have shown that H_4R activation has a pro-inflammatory effect. Activation of microglia was mediated by both the H_1R and the H_4R and led to the augmentation of the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Dong et al. 2014; Zhang et al. 2020). This observation is in agreement with in vivo data showing that *intracerebroventricular (ICV)* infusion of an H_4R agonist increased the total microglia cell number and the density of ramifications as

indicated by the marker ionized calcium-binding adaptor moleculei1 (Iba-1) in wild-type mouse brains (Frick et al. 2016). The same study also showed that an H_4R antagonist blocked the effects of histamine on microglial cells (Frick et al. 2016).

2 Neurological Diseases and H_4R

2.1 Parkinson's Disease (PD)

The second-most prevalent neurodegenerative disease is PD. The motor symptoms of PD are mainly caused by the loss of dopaminergic neurons in the substantia nigra (Hirsch et al. 1988; Damier et al. 1999). PD is characterized by the tremor in rest, bradykinesia, rigidity, flexed posture loss of postural reflexes, and freezing of gait (Sulzer 2007). A neuropathological hallmark of the disease is the presence of α-synuclein accumulation, Lewy bodies and Lewy neurites in multiple brain areas (Braak et al. 2003; Shan et al. 2012b). We found that in an unbiased RNA-sequencing of the postmortem human basal ganglia, H_4R was strongly upregulated in the substantia nigra of PD patients (Fang et al. 2020), which is in line with the results of our previous independent qPCR analyses which showed a 4.3–6.5-fold upregulation of H_4R-mRNA in the basal ganglia of PD patients (Shan et al. 2012a). Not only our previous postmortem observations, but also others found increased density of histaminergic fibers in the substantia nigra (Anichtchik et al. 2000) and enhanced histamine levels in both the substantia nigra and the putamen of PD patients (Rinne et al. 2002) and were confirmed by a targeted gene-set enrichment analysis using the ROAST test, a hypothesis-driven analysis (Fang et al. 2020). In addition, gene-set enrichment and pathway analyses of transcriptome-wide RNA-sequencing results showed that H_4R was in the top-four functional categories of "neuroactive ligand–receptor interaction" for PD treatment targets (Fig. 1) (Fang et al. 2020). Little information is available on the associations between H_4R and PD, except that the top three from the list, gastric inhibitory polypeptide receptor, adrenoceptor alpha 2B, and purinergic receptor P2X7, have been recognized as potential treatments of PD (Savola et al. 2003; Mittal et al. 2017; Athauda et al. 2017; Searles Nielsen et al. 2018) (ClinicalTrails.gov Id: NCT03918616).

The postmortem study does not allow us to conclude whether the H_4R is a potential target for treatment of the disease. A translational PD model, the rotenone-lesioned rat model, exhibited a strong degeneration of dopaminergic neurons in the substantia nigra, PD neuropathology and α-synuclein accumulation (Betarbet et al. 2000; Cicchetti et al. 2009), as well as strongly increased H_4R-mRNA levels in the substantia nigra (Zhou et al. 2019). Intracerebroventricular administration of the H_4R antagonist JNJ7777120 ameliorated the degeneration of dopaminergic neurons in the substantia nigra of this PD rat model. The protective effects were also supported by the reduction of α-synuclein accumulation in both substantia nigra and striatum (Zhou et al. 2019; Fang et al. 2020). Thus, blocking the H_4R plays a protective role in rotenone-lesioned PD rats. JNJ7777120 acts through the inhibition of the pro-inflammatory phenotype of microglia (Zhou et al. 2019).

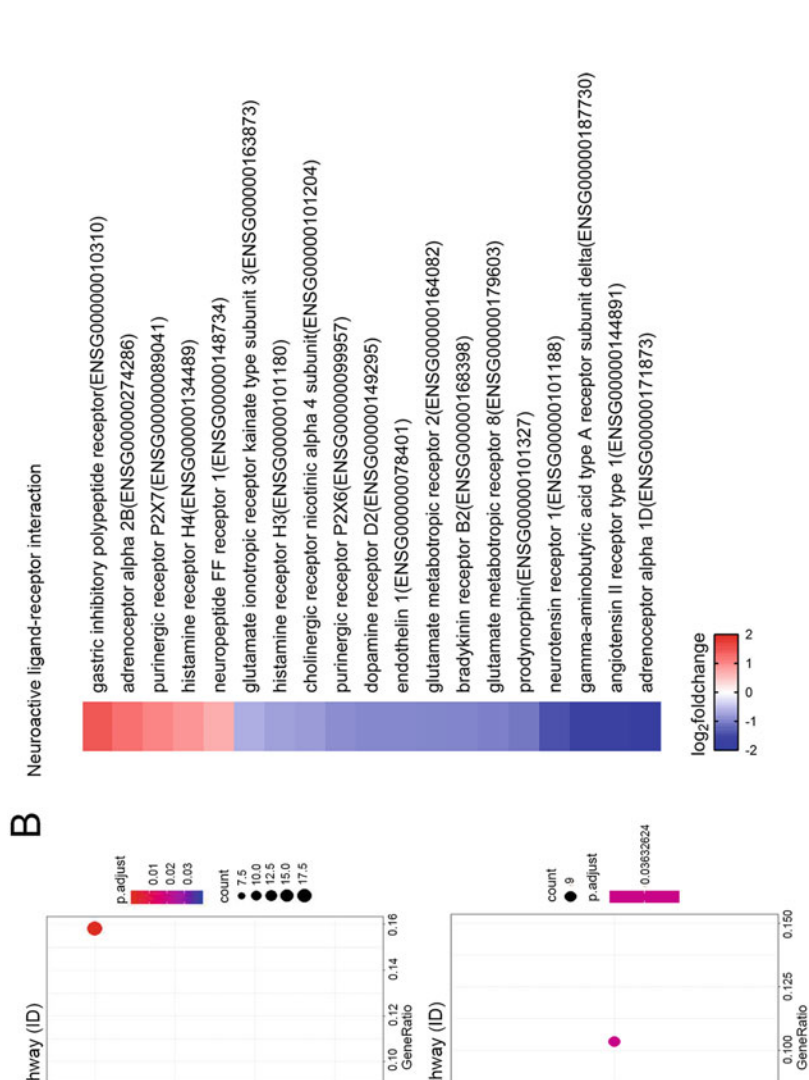

Fig. 1 Biological pathways enriched in both substantia nigra and putamen from PD patients relative to controls. Enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) biological pathways mapped from 39 top upregulated and 41 top downregulated transcripts in the substantia nigra (**a**) and in the putamen (**c**) of PD patients relative to controls. (**b**) Heatmap showing the $\log_2$ fold expression changes of the genes differentially expressed in PD substantia nigra and being in the top-enriched KEGG pathway "Neuroactive ligand–receptor interaction" (Fig. 1 (Fang et al. 2020) with permission)

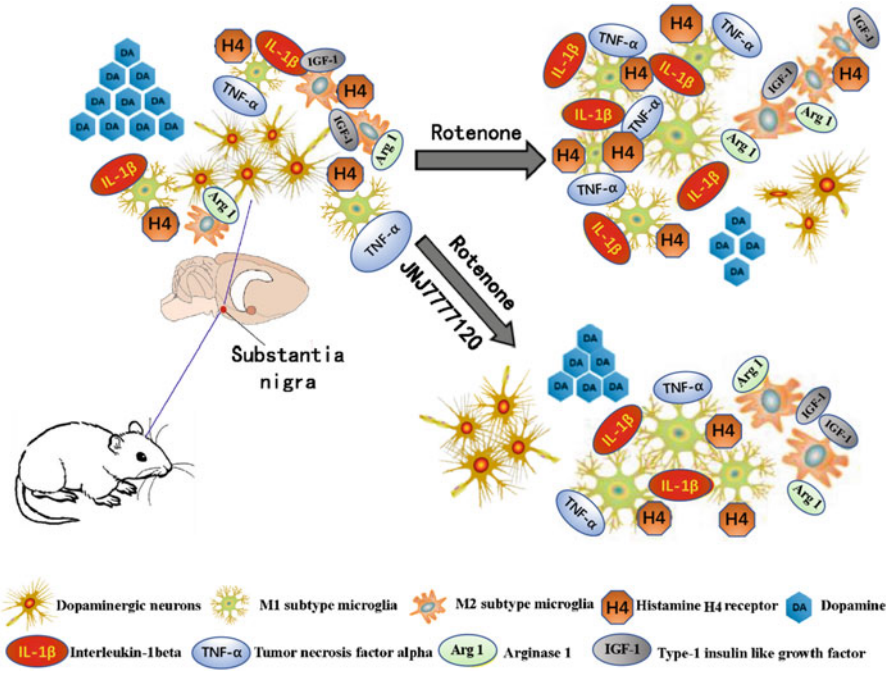

Fig. 2 Schematic of the effects of H_4R antagonist JNJ7777120 on the rotenone-lesioned PD rat model. JNJ prevents dopaminergic neuron degeneration and dopamine level diminishment in the rotenone-lesioned PD rat model by reducing the pro-inflammatory phenotype of microglia (marked by IL-1β and TNF-α) but not the neuroprotective phenotype of microglia (marked by Arg1 and IGF-1) (Fig. 9 (Zhou et al. 2019) with modifications and permission)

Reductions in the number of Iba-1-positive microglia in the substantia nigra, as well as the size of microglia in the striatum, were observed in the JNJ7777120-treated rotenone-induced PD rat model (Zhou et al. 2019; Fang et al. 2020). In addition, the H_4R antagonist inhibited the pro-inflammation phenotype of microglia (marked by reduced expression of IL-1β and TNF-α at both mRNA and protein levels), while not affecting the neuroprotective phenotype of microglia (marked by arginase-1 (Arg1) and insulin-like growth factor-1 (IGF-1)) (Zhou et al. 2019) (Fig. 2).

On the other hand, not only the dopamine level, but also alterations of γ-aminobutyric acid (GABA)ergic and cholinergic tones, and a reduced serotonin level have been associated with motor symptoms of PD (Qamhawi et al. 2015; Lozovaya et al. 2018). There was no information regarding the effect of blocking the histamine receptor H_4R on the levels of neurotransmitters in the basal ganglia. We showed for the first time that the H_4R antagonist rescued dopamine levels and recovered levels of serotonin and its main metabolite 5-hydroxyindoleactic acid in

basal ganglia of the PD rat model without influencing glutamine and acetylcholine levels (Fang et al. 2020).

Therefore, the results of both the postmortem human brain (Shan et al. 2012a) and the preclinical animal model studies (Zhou et al. 2019; Fang et al. 2020) indicated that blocking the H_4R might provide a promising therapeutic target for PD treatment.

2.2 Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease with fast disease progression and characterized by motor neuron loss, leading to respiratory insufficiency and death after 3–5 years (Hardiman et al. 2017). Multi-omics-based data have indicated that the histaminergic system is dysregulated in sporadic ALS. In particular, genome-wide analysis has shown multiple genomic variations in H_4R single nucleotide polymorphisms in non-familial ALS patients (Apolloni et al. 2019). H_4R-mRNA is dysregulated together with other histaminergic gene transcripts in the two subgroups of sporadic ALS patients (sALS1 and sALS2) (Apolloni et al. 2017, 2019) that were based on transcriptome analysis and separated by unsupervised hierarchical clustering (Aronica et al. 2015). The cortical mRNA expression studies showed that H_4R was downregulated in sALS1 and was upregulated in sALS2 compared to healthy individuals (Apolloni et al. 2017). This sALS2 finding is in line with the observed approximately 1.5-fold increase of H_4R protein level in the cortex of an ALS mouse model, the pre-symptomatic phase of the copper-zinc superoxide dismutase 1 SOD1-G93A mutant (Volonté et al. 2019).

Increased activation and an increase in the number of microglia are a hallmark of ALS pathology and may contribute to motor neuron degeneration (Boillée et al. 2006; Chiot et al. 2020; Spencer et al. 2020). In line with this pathology, inhibiting the inflammatory response of microglia in ALS animal models robustly slowed the course of the disease (Boillée et al. 2006; Chiot et al. 2020). Histamine induced a reduction of the microglial inflammatory markers nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and an increase in Arg1 and P2Y12 receptor in primary cultures of microglia from SOD1-G93A mice. The H_4R antagonist JNJ7777120 brought the microglial NF-kB levels back to control levels (Apolloni et al. 2017). Furthermore, this anti-inflammatory effect was mainly elicited by the H_4R, and not the H_3R, because the H_4R antagonist JNJ7777120, but not the H_3R antagonist thioperamide, significantly blocked the NOX2 and Arg1 effects in the microglia of the ALS mouse model (Apolloni et al. 2017). Together, these results indicate that blocking the H_4R might be a promising approach to reduce the ALS-specific activation of microglia, a conclusion that warrants future tests in the preclinical animal models.

3 Concluding Remarks and Future Perspectives

H_4R is involved in the regulation of BBB permeability and microglial activity, which are both dysfunctioning in neurodegenerative diseases. Data from transcriptional analyses and human GWAS indicate that H_4R is linked to neurodegenerative diseases. Specifically, H_4R-mRNA is highly upregulated in the basal ganglia of PD patients (Shan et al. 2012a; Fang et al. 2020) and H_4R single nucleotide polymorphisms are strongly associated with sporadic ALS patients (Apolloni et al. 2019). Transcriptomic analysis of subgroups of sporadic ALS patients (sALS1 and sALS2) showed that H_4R-mRNA is downregulated in sALS1 and upregulated in sALS2 (Volonté et al. 2019).

Translational animal models have been used to study H_4R function and preclinical efficacy in the treatment of PD and ALS. An H_4R antagonist alleviated dopaminergic neuron degeneration and α-synuclein neuropathology in both substantia nigra and striatum of a PD animal model. These protective effects were largely elicited by inhibiting the pro-inflammatory phenotype of microglia and did not affect the neuroprotective phenotype of microglia. Furthermore, the same H_4R antagonist significantly blocked inflammatory markers in microglia of an ALS mouse model. Current knowledge of the potential therapeutic effects of H_4R ligands in brain is still in an early explorative phase. Nevertheless, analysis of the current literature and our own experimental data as well as the emergence of disease-associated microglia showing unique transcriptional and functional signatures in PD and ALS (Deczkowska et al. 2018) all point out that the H_4R may represent a promising target for the treatment of central nervous system diseases.

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