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Histamine beyond its effects on allergy: Potential therapeutic benefits for the treatment of Amyotrophic Lateral Sclerosis (ALS)

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ABSTRACT

ALS currently remains a challenge despite many efforts in performing successful clinical trials and formulating therapeutic solutions. By learning from current failures and striving for success, scientists and clinicians are checking every possibility to search for missing hints and efficacious treatments. Because the disease is very complex and heterogeneous and, moreover, targeting not only motor neurons but also several different cell types including muscle, glial, and immune cells, the right answer to ALS is conceivably a multidrug strategy or the use of broad-spectrum molecules. The aim of the present work is to gather evidence about novel perspectives on ALS pathogenesis and to present recent and innovative paradigms for therapy. In particular, we describe how an old molecule possessing immunomodulatory and neuroprotective functions beyond its recognized effects on allergy, histamine, might have a renewed and far-reaching momentum in ALS.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a predominant motor neuron disease that irreversibly targets upper and lower motor neurons. Upper motor neurons carry motor information from the motor cortex through the brainstem and spinal cord to the lower motor neurons, which in turn directly signal to the muscles (Brown & Al-Chalabi, 2017). The loss of somatic motor neurons leads to paralysis that culminates into respiratory failure and death. ALS has a worldwide incidence estimated at 1.75/100.000 person-years of follow-up (PYFU), 2.03/100.000 in men and 1.45/100.000 in women (Marin et al., 2017). Heterogeneity is identified in ALS incidence, for instance, between North Europe-North America-New Zealand (pooled standardized incidence of 1.81/100.000/PYFU), with regard to East Asia (0.83/100.000 PYFU) or South Asia (0.73/100.000/PYFU). Moreover, there is variation with age (characterized by a progressively increased incidence from the 40s, with a peak in the 60s–70s, followed by a sharp decrease) and with a consistency of age-specific incidence that varies within different subcontinents (Marin et al., 2018).

In the majority of cases, ALS occurs as a sporadic form, while approximately 10–% of patients suffer from a familial disease attributed to

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale–revised; CNS, central nervous system; HA, histamine; HD, Huntington's disease; PD, Parkinson's disease; MS, multiple sclerosis.

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dominant, high-penetrance gene variants. >25 genes have been identified, which are responsible for approximately 60% of familial forms and 10% of sporadic forms. The most common genetic mutations known to cause ALS are located in the following genes: *C9ORF72* (40% of familial cases, 5–10% of sporadic), *SOD1* encoding superoxide dismutase 1 (20% of familial cases and 2% of sporadic cases), *fused in sarcoma/translated in liposarcoma* (*FUS*, also known as *TLS*, 5% of familial cases, 1% of sporadic cases) and *TARDBP* (5% of familial cases, 1% of sporadic cases). Significant advances were recently made in the molecular comprehension of the etiopathogenesis of the disease, although the whole process of motor neuron death and motor impairment remains a major challenge in ALS.

In addition to excitotoxicity, the first identified abnormality, the ALS mechanisms include oxidative stress, metabolism impairment, protein misfolding and aggregation, cytoskeletal disorganization and defective axonal transport, reduced nucleocytoplasmic trafficking, endoplasmic reticulum stress and compromised autophagy, impaired RNA metabolism, and miRNA dysregulation (Taylor, Brown, & Cleveland, 2016). Most importantly, these pathogenic events occur not only in motor neurons and their glial partners but also in multiple tissues and cell types comprising the immune and muscle cells, thus justifying the multisystem and non-cell-autonomous nature of the disease (Chen et al., 2018); (Hardiman et al., 2017). Regrettably, the pathological derangement of the cross-talk between neuronal and non-neuronal cells is incompletely understood, and this might be one possible explanation for therapeutic failures (Serio & Patani, 2018). Recently, cortical hyperexcitability and decreased intracortical inhibition have been considered as contributory to the disease (Van den Bos et al., 2018). Indeed, hyperexcitability in the motor cortex, even in the absence of clinical weakness, induces trans-synaptic motor neuron degeneration in the anterior horns of the spinal cord through anterograde glutamate-mediated excitotoxicity (Mills & Nithi, 1997). In addition, decreased intracortical GABA inhibition has also been identified, further rendering motor cortex neurons hyperexcitable and susceptible to death in ALS (Medelin et al., 2016). However, these paradigms are not sufficient to explain the complexity of upper and lower motor neuron degeneration, and the emerging general explanation is that a convergence of multiple pathological events is responsible for the onset and progression of the disease.

Among these events, an unbalance within the wide range of inducers, sensors, and mediators that form the regulatory network of a neuroinflammatory process contributes to motor neuron degeneration in ALS. Inducers initiate the inflammatory response by activating specialized sensors, which in turn stimulate the production of specific sets of mediators. The inflammatory mediators then alter the functional state of the target cells, the motor neurons within the motor cortex, and ventral horns of the spinal cord in ALS, in a way that should allow an adaptive process. However, in the absence of adaptation and resolution of the inflammatory process, this regulatory network generates an invasive cycle of degeneration that in ALS culminates with motor neuron loss. Thus, inflammation constitutes another important mechanism that can tip the balance between protection and neuronal loss, and the expression of a pro-inflammatory phenotype by microglia plays a central role in this process (Liu & Wang, 2017).

Microglia are generally found to accumulate at sites of cellular damage, with the main task of scavenging dead cells and secreting neuron survival factors. However, inappropriate prolonged activation of microglia can cause unbalanced responses, further leading to CNS injury and motor neuron death (Lall & Baloh, 2017). It was proposed that microglia in ALS are often primed by former pathological insults, genetic predisposition, or environmental stressors to respond more vigorously to a subsequent inflammatory stimulation. Thus, inflammatory microglia contribute to boosting and propagating the neurodegenerative process, with the cooperation of astrocytes and peripheral immune signaling to the CNS by mast cells and infiltrated monocytes/macrophages (Lam et al., 2016; Trias et al., 2017) but with the contrasting action of regulatory and effector T cells (Sheean et al., 2018; Thonhoff, Simpson, & Appel, 2018). The elucidation of the signaling pathways that induce hyperactivation of microglia highly contributes to shed light on the complex cellular and molecular regulatory networks of ALS pathology.

Among the constitutively bioactive molecules with recognized regulatory roles in neurotransmission and immune responses in the CNS, the endogenous biogenic amine histamine (HA), the prototype molecule mediating peripheral allergic reactions, is well known to induce activation of microglia and to regulate critical functions including chemotaxis, phagocytosis, and cytokine secretion *in vitro* and *in vivo*.

With focus on the documented impact of HA on conditioning the inflammatory profile of microglia (Thonhoff et al., 2018), the aim of this review is to gather the most recent information and discuss about the emerging role that HA might assume in ALS pathogenesis. We propose that the histaminergic modulation might become a candidate mechanism for understanding ALS insurgence, progression, and therapy. The idea that histaminergic drugs might be proven to work also in ALS could appear either provocative or appealing but surely deserving deeper scientific consideration.

2. Current therapeutic strategies in ALS

ALS is a relentless disease typically causing death within 3–5 years from the onset. Despite decades of extensive research and randomized controlled clinical trials, almost all efforts aimed at identifying a successful treatment regimen have failed thus far. Genetic heterogeneity, diagnostic delay, poor clinical trial design or rationale, insufficient animal models, and lack of reliable biomarkers are among the potential reasons limiting significant development in clinical trials (Katyal & Govindarajan, 2017). Presently, there are only two FDA-certified drugs: i) riluzole (Rilutek®, Teglutik®, approved back in 1995), an anti-glutamatergic drug that has shown to prolong survival at most by 2–3 months; ii) edaravone (Radicava®, Radicut®), which was approved in Japan in 2015 and in the USA in 2017 based on a modest, although statistically significant, result of randomized controlled clinical trials performed with patients at early-stage ALS. However and regrettably, none of these drugs are fully satisfactory, and new ideas are mandatory for supporting further studies and formulating more effective treatments.

2.1. Approved drug edaravone

Edaravone is the first new drug approved by the FDA for the treatment of ALS since many years. It is reported to confer protection against oxidative stress through its electron-donating properties, based on studies performed both *in vitro* and *in vivo* on neuron, glial, and vascular endothelial cells (Takei et al., 2017). Although the mechanisms by which edaravone might be effective were unknown during its approval and also currently, the edaravone clinical program was developed as a multistudy series spanning 16-plus years and involving randomized clinical trials, extension trials, and *post hoc* analysis, with the final goal of providing effective treatments to ALS patients. The study MCI 186-19 was the culmination of a 13-year edaravone clinical development program. In particular, in a randomized controlled study, a total of 137 patients were recruited, 69 in the edaravone and 68 in the placebo group. The results showed that the mean change in ALSFRS-R scores for the edaravone group was -5.01 ± 0.64 compared with that of -7.50 ± 0.66 for the placebo group. There was a statistically significant least-squares mean difference in ALSFRS-R scores between the 2 groups, representing 33% less functional loss in patients treated with edaravone than those who received placebo during the course of 24 weeks. The benefits and safety of edaravone in the treatment of ALS were then re-evaluated in a recent meta-analysis study demonstrating that intravenous edaravone is efficacious in ALS patients with no severe adverse effects (Luo, Song, Li, Huiwang, et al., 2019). Notwithstanding these

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promising results, additional reliable randomized controlled trials with larger sample sizes will further assess the efficacy and safety of edaravone in ALS.

2.2. New drugs under trial

>50 clinical trials with potential ALS drugs have failed thus far, and there is a continuous intense search for treatments (Table 1). Here, we provide a brief description of only those compounds currently in interventional clinical trials of phase-III and independently from the recruitment status of the trials.

Tauroursodeoxycholic acid (TUDCA) is a unique bile acid derivative that acts as a potent antiapoptotic agent. TUDCA has been shown to restore the function of motor neurons by stabilizing the mitochondrial membrane, inhibiting nitrite production, and preventing the activation of matrix metallopeptidase 9 (Vaz et al., 2015). The neuroprotective effects of this compound are confirmed in human stem cell-derived motor neurons carrying a mutated SOD1 allele. Moreover, the administration of TUDCA in SOD1-G93A mice reduces muscle denervation (Thams et al., 2019). In addition to the SOD1-G93A model, TUDCA has shown promising effects also in the C9ORF72 model by providing protection against poly(GA)-induced toxicity, a pathogenic mechanism implicated in the neurodegenerative processes of C9FTD/ALS (Zhang et al., 2014).

In patients, a pilot study has provided preliminary clinical data indicating that TUDCA is safe and may be effective in slowing ALS progression (Elia et al., 2016). TUDCA is currently under investigation in a Phase-III clinical trial for ALS patients.

Methylcobalamin is a vitamin B12 analog that effectively and dose dependently prevents embryonic stem cell-derived motor neuron death induced by co-culturing conditions with SOD1-G93A astrocytes. Moreover, treatment with methylcobalamin together with the conventional ALS drug riluzole further enhances survival of motor neurons in this *in vitro* ALS system (Ito, Izumi, Niidome, & Ono, 2017). In the wobbler mouse characterized by cellular transport defects, neurofilament aggregation, neuronal hyperexcitability, and neuroinflammation, thus showing striking similarities to ALS, methylcobalamin at a very high dose of 30 mg/kg significantly inhibits denervation muscle atrophy and motor axonal loss by attenuating motor symptoms (Ikeda, Iwasaki, & Kaji, 2015). In patients with ALS, previous reports have suggested that administration of high-dose methylcobalamin could have clinically beneficial effects (Izumi & Kaji, 2007). Moreover, the results of a recent study have shown that although an ultra-high dose of methylcobalamin has not demonstrated significant efficacy in patients with ALS, the treatment may prolong survival and delay disease progression if started early (≤12 months of duration) (Kaji et al., 2019). Methylcobalamin is currently under investigation in a Phase-III clinical trial for patients with ALS.

Masitinib is a type-3 tyrosine kinase inhibitor known to modulate neuroinflammatory features associated with many neurodegenerative disorders. In microglia cultures from symptomatic SOD1-G93A spinal cords, masitinib prevents colony-stimulating factor 1 receptor-induced proliferation, cell migration, and the expression of inflammatory mediators. Treatment with masitinib started after the onset of paralysis in SOD1-G93A rat prolongs post-paralysis survival and decreases the number of aberrant glial cells, microgliosis, and motor neuron pathology in the spinal cord (Trias et al., 2016). Moreover, masitinib prevents the excessive accumulation of mast cells in the skeletal muscles of symptomatic SOD1-G93A rats and delays neuromuscular junction denervation (Trias et al., 2017; Trias et al., 2018). Results of phase-II/III trials on patients with ALS have confirmed that the study has met its primary end point, demonstrating a potential therapeutic benefit for masitinib (Kiernan, 2018). Masitinib is currently under investigation in a Phase-III clinical trial for patients with ALS.

Cannabidiol (CBD) is one of the >100 pharmacologically bioactive compounds defined as cannabinoids that can be isolated from the *Cannabis sativa* plant. Because it does not possess the psychoactive properties of other cannabis-related compounds, cannabidiol holds a considerable therapeutic potential. By binding to specific receptors, cannabinoids have shown antioxidant, anti-inflammatory, and neuroprotective effects in many preclinical models of neurodegenerative diseases, which include ALS. In many studies on the SOD1-G93A model, cannabinoids have reported neuroprotective activity, delaying disease progression and motor impairment and prolonging survival of the animals. In patients with ALS, studies that aimed at investigating the effect of cannabinoids have only focused on the alleviation of ALS-related symptoms, not on the control of disease progression. In a proof-of-concept trial, nabiximols (a specific extract of *Cannabis*) has shown a positive effect on spasticity symptoms in patients with ALS, with an acceptable safety and tolerability profile (Riva et al., 2019). Cannabidiol is currently under investigation in a Phase-III clinical trial for patients with ALS.

Arimoclomol is a hydroxylamine derivative acting as a co-inducer of heat shock proteins expression that is found effective in delaying disease progression and extending the lifespan of SOD1-G93A mice even when administered at the symptomatic phase (Kalmar et al., 2008). Indeed, pharmacological activation of the heat shock response is considered a successful therapeutic approach for treating ALS. Enhanced heat shock proteins expression not only affects protein aggregation but can also lead to more effective clearance of protein aggregates, by triggering the proteasome-ubiquitin system or autophagy responses (Kalmar, Lu, & Greensmith, 2014). Not surprisingly, arimoclomol-treated SOD1-G93A mice have shown a clear improvement of muscle function and motor neuron survival (Kieran et al., 2004), together with a decrease in the number of ubiquitin-positive aggregates in the spinal cord, and an improvement in neuromuscular function (Kalmar, Edet-Amana, & Greensmith, 2012). In patients with ALS, arimoclomol has shown good safety record (up to 300 mg/day) for a short period of time (12 weeks) and a good penetration across the blood–brain barrier (Cudkowicz et al., 2008). A Phase-II study has clearly shown that arimoclomol is safe and well tolerated at a dosage of 200 mg three times a day for up to 12 months. Although not powered for therapeutic effect, the results of this study suggest a perspective therapeutic benefit of arimoclomol (Benatar et al., 2018). Arimoclomol is currently under investigation in a Phase-III clinical trial for ALS patients.

In addition to these studies, additional and innovative approaches are currently tested for treating ALS, as, for instance, the use of gene silencing in cases where a genetic cause of ALS is identified and the corresponding transcript or protein is assumed to exert toxic activities. In particular, the strategies trying to suppress or alleviate the toxic actions of etiologic ALS genes include targeted ablation of the defective gene transcript by antisense oligonucleotides or microRNA, DNA mutagenesis reverting the defective gene to its wild-type form in the appropriate non-germline cells, interference with the transcriptional process by the use of small molecules, immune-mediated neutralization of the mutant protein, and mesenchymal stromal cells as an autologous stem cell therapy. Clinical trials investigating the use of antisense oligonucleotides to

Table 1
Ongoing Phase-III interventional trials on ALS.

Compound	Target/mechanism	Recruiting	Identifier
Tauroursodeoxycholic acid	Anti-apoptotic	Not yet	NCT03800524
Methylcobalamin	B_{12} vitamin derivative	Yes	NCT03548311
Masitinib	Tyrosine kinase c-Kit inhibitor	Not yet	NCT03127267
CannTrust CBD Oil	Active cannabinoid	Yes	NCT03690791
Arimoclomol	Stimulates repair pathways	Yes	NCT03491462
Levosimendan	Calcium channel sensitizer	Yes	NCT03505021
Deferiprone	Iron chelator	Not yet	NCT03293069
MSC-NTF cells	Mesenchymal cell therapy	Yes	NCT03280056

Search query: ALS (Amyotrophic Lateral Sclerosis) https://clinicaltrials.gov/ Filtered for: Status: Recruiting – Not yet recruiting – Active, not recruiting – Enrolling by invitation; Study type: Interventional (Clinical Trial); Study Phase: Phase-III.

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silence SOD1 and C9ORF72 have already begun. The strong rationale and the positive results from an interim analysis of Phase-I clinical trial with antisense oligonucleotide for treating ALS caused by SOD1 mutations (unpublished data) provide hope for opening a new era in the treatment of ALS.

Several treatments that are not discussed in this work are presently under scrutiny in clinical trials of Phase-I/II: for details, please refer to https://clinicaltrials.gov/.

3. Pleiotropic actions and signaling of histamine in the CNS

HA has been a milestone in pharmacology and immunology since 1910 when Sir Henry Dale and Patrick Laidlaw identified its potent physiological actions (Dale & Laidlaw, 1910). The Nobel Prize in Physiology and Medicine was then awarded twice for HA-related drugs, in 1957 to Daniel Bovet for the discovery of antihistamines (anti-H1R) and in 1988 to Sir James Black for the discovery of anti-H2R antagonists. While H1R, H2R, and H4R antagonists have revolutionized the available therapies for allergic, gastric, and immune disorders, H3R antagonists have more recently entered clinical trials for applications in obesity and a large variety of neurological disorders (Cataldi, Borriello, Granata, Annunziato, & Marone, 2014; Ghamari et al., 2019).

Given the large array of biological functions directly regulated by HA that furthermore is mirrored by the widespread projections of histaminergic neurons in the brain, we expect that the targets for HA therapy might even increase in the near future.

3.1. Histamine metabolism and physiology

In eukaryotic cells, the rate of HA synthesis is determined by the bioavailability of L-histidine that is taken up by the cells through the L-amino acid transporter system. HA is synthesized exclusively by decarboxylation of L-histidine by histidine decarboxylase (HDC). Once synthetized inside the cells, the vesicular monoamine transporter VMAT-2 is then responsible for the internalization of HA into vesicles. HA is then secreted in the microenvironment by exocytosis, upon stimulation, and is catabolized by the extracellular enzymes HA *N*-methyltransferase (HNMT) or diamine oxidase (DAO). The enzymes responsible for the transport and metabolism of HA are ubiquitous proteins in the nervous system.

In the CNS, the sources of HA include mast cells, neurons, and microglia (Katoh et al., 2001), while peripherally, HA is produced and secreted by basophils, neutrophils, monocytes, macrophages, dendritic cells, platelets, enterochromaffin-like cells, and gastrin-containing cells. HA neurotransmission follows the circadian rhythm, and HA is released throughout the brain with a daily rhythm characterized by peak release during wakefulness and relatively lower levels during sleep. Most of HA release is nonsynaptic, thus implying a wide diffusion through a concentration gradient. A nonsynaptic diffusion of HA is furthermore consistent with the features of the selective metabotropic receptors for HA, H1R-H4R, which act through "slow" transmission mechanisms requiring the production of intracellular second messengers. Combined with an abundant expression of H1R-H4R receptors, this suggests a profuse and widespread histaminergic control of neural circuit activity (Bolam & Ellender, 2016).

H1R-H4R receptors are differentially expressed in the CNS by immunocompetent cells, neurons, astrocytes, microglia, and endothelial cells. The downstream pathways triggered after binding of HA comprise the activation of G-proteins (Gαq/11, Gsα, and Gαi/o) and phospholipase C, leading to inositol triphosphate-dependent release of calcium from intracellular stores and diacylglycerol formation with modulation of voltage-dependent calcium channels. Activation of adenylyl cyclase and stimulation of phospholipase A2 with arachidonic acid production also occur, with activation of kinases, among which mitogen-activated protein kinases, protein kinase B, glycogen synthase kinase 3, protein kinase A, AMP-kinase. Cyclic AMP-dependent response element-binding protein, and NF-κB activation generally follows, with production of nitric oxide and cyclic GMP through nitric oxide-dependent guanylyl cyclase. Through these mechanisms, HA triggers several distinct responses in the target cells culminating in early and late gene expression modulation and control of several physiopathological functions.

H1R-H3R are the receptors most expressed in the brain, whereas H4R is mainly present peripherally on immune cells modulating neutrophil release, eosinophil shape, and mast cell chemotaxis during an inflammatory insult (Thurmond, 2015). In the CNS, H1R activation is linked to excitatory stimulation, responsible for controlling nutritional state and wake–sleep cycles, and, moreover, found involved in neuroinflammatory processes (Fukui et al., 2017). Mutant mice lacking the H1 receptor show defective locomotor and exploratory behaviors (Parmentier et al., 2016; Yanai et al., 1998). H2R regulates gastrointestinal secretion, muscle relaxation, vasodilation, and neutrophil activation, playing a role in neuronal plasticity, hippocampal synaptic transmission, and cognitive performance (Monczor & Fernandez, 2016). H3R is the most abundant HA receptor in the CNS, expressed by neurons, astrocytes, microglia, and oligodendrocyte precursors (Garcia-Galvez, Arias-Montano, Morales-Figueroa, Nieto-Alamilla, & Marquez-Gomez, 2016; Haas, Sergeeva, & Selbach, 2008). H3R is involved in cognitive processes, and activation of this receptor promotes wakefulness (Schlicker & Kathmann, 2017). Both synthesis and release of HA in the CNS are under the control of presynaptic H3R located on neuronal soma and axonal varicosities. H3R, moreover, behaves as an autoreceptor by inhibiting the synthesis and release of HA and also as a heteroreceptor inhibiting other neurotransmitters such as dopamine, serotonin, noradrenaline, GABA, glutamate, and acetylcholine (Deng, Weston-Green, & Huang, 2010). Blockade of H3R in the CNS results in increased synthesis and release of HA (Brabant, Charlier, & Tirelli, 2013).

In microglia, the activation of H1R-H4R receptors controls basic functions such as migration, phagocytosis, and release of cytokines/chemokines (Barata-Antunes, Cristóvão, Pires, Rocha, & Bernardino, 2017). Accumulating evidence under *in vitro* and *in vivo* inflammatory conditions indicates that HA exerts beneficial effects by stimulating anti-inflammatory actions in microglia (Apolloni et al., 2017). HA deficiency instead reduces the neuroprotective role of microglia *in vivo* and inhibits cell ramifications and expression of IGF-1 through the H4R (Frick, Rapanelli, Abbasi, Ohtsu, & Pittenger, 2016). In addition, the HA precursor histidine through H1R, but not H2R, inhibits microglia activation and IL-1β upregulation in lumbar spinal cord, also alleviating mechanical allodynia and thermal hyperalgesia after partial sciatic nerve ligation in rats (Yu et al., 2016). On the other hand, HA triggers microglial phagocytosis through H1R activation and ROS production through H1R and H4R activation, and injection of HA in the *substantia nigra* of adult mice *in vivo* induces dopaminergic neurotoxicity through H1R (Rocha et al., 2016). Activation of H3R instead inhibits chemotaxis in hippocampal slices and in primary microglia in culture, phagocytosis in prefrontal cortex, proinflammatory cytokine production, and improves depression-like behavior in the mouse tail suspension test (Iida et al., 2015; Iida et al., 2017). These results clearly establish a dual role for HA in microglia, respectively, pro-inflammatory during basal conditions, while anti-inflammatory under inflammatory and pathological states (Barata-Antunes et al., 2017).

Astrocytes cooperate to neuronal functions through numerous cell-to-cell interactions and are involved in several neurological disorders. Recent knowledge has established that HA can influence also some key astrocytic activities during health and disease conditions, such as ion homeostasis, energy metabolism, neurotransmitter clearance, neurotrophic activity, and immune response. These processes are mediated through the HA receptor subtypes, H1R, H2R, and H3R, abundantly expressed by astrocytes (Jurič, Kržan, & Lipnik-Stangelj, 2016). Negative regulation of astrocytic TNFα and IL-1β production and the enhancement of astrocytic GDNF are also stimulated by HA as H1R-H3R receptor-mediated processes (Xu et al., 2018). Moreover, HA activates human astrocytoma cells signaling through histamine H1R and H2R,

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leading to distinct cellular responses. Activation of H1R causes concentration-dependent release of [Ca2+] from internal stores and concentration-dependent increase in glutamate release. H2R activation increases cyclic adenosine monophosphate levels and phosphorylation of transcription factor cAMP response-element binding protein, thus emphasizing a role for HA in neuron-glia communication (Kárpáti et al., 2018).

HA neurons are found merely in the tuberomamillary nucleus of the posterior hypothalamus, from where they project their axons all over the CNS and spinal cord in rats, mice, and humans (Blandina, Munari, Provensi, & Passani, 2012). Two main bundles of axons from the tuberomamillary nucleus send a large arborization, for instance, to the cortex, and most cortical regions receive a moderately dense and sparse histaminergic input. Among these regions, the primary motor cortex (containing giant pyramidal Betz cells or upper motor neurons) is a key structure that receives abundant histaminergic projections. Upper motor neurons then send their axons down to the spinal cord through the corticospinal tract, where in humans, they synapse directly with anterior horn cells (the lower motor neurons), which, in turn, synapse directly with their target muscles. Importantly, HA directly excites rat spinal motor neurons through H1R and H2R by increasing their excitability, affecting membrane input resistance, and potentiating their repetitive firing behavior. In this way, the hypothalamus-spinal cord histaminergic fibers directly modulate final motor outputs and actively regulate ongoing motor execution and spinal motor reflexes (Wu et al., 2012). The elaboration of motor responses into different behavioral states, motor plans, voluntary movements, and motor skills actually relies on the ability of selecting appropriate motor outcomes according to specific environmental inputs, and HA with its receptors actively participates to this modulation of motor control. It is now important to recall and emphasize that both upper and lower motor neurons are the exclusive targets of neurodegeneration and motor impairment during ALS.

In addition to motor circuits, histaminergic neurons provide a variety of different signaling mechanisms to the brain. HA directly controls key functions such as the sleep-wake cycle, aggression, feeding, nociception, learning, and memory. Of note, several of the physiological roles of HA are correlated to its capacity to potentiate the excitability of most CNS neurons, and for this reason, HA is rightly considered a regulator of "whole brain" activity. In addition to these neuronal effcts, HA regulates the multidirectional information that maintains a proper balance between the CNS and peripheral immune functions. Indeed, the CNS promptly responds to several peripheral inflammatory reactions, CNS alterations are often translated into peripheral immune changes, and HA is the master molecule of this neuroimmune regulation (Cacabelos, Torrellas, Fernández-Novoa, & Aliev, 2016) that, of note, plays a central role also in ALS.

3.2. Role of histamine in disease pathology

As proven by human post-mortem and animal studies, the HA system is highly implicated and becomes altered in the diseased CNS, for instance, after ischemia; traumatic brain and spinal cord injury; Alzheimer's (AD), Huntington's (HD), and Parkinson's (PD) diseases; multiple sclerosis (MS); and Wernicke's encephalopathy (for a comprehensive review, consult: Hu & Chen, 2017; Ghamari et al., 2019). Moreover, HA deficiency has been directly implicated as a cause of Tourette syndrome and may contribute to neuropsychiatric conditions comprising schizophrenia, as well as narcolepsy, food intake, and sleep disorders.

For instance, in cerebral ischemia, a particular value for treatment is provided by HA able to act on multiple cellular targets. After middle cerebral artery occlusion inducing focal ischemia in the cortex and striatum, the release of HA from histaminergic neurons and from degranulating mast cells accumulated in the ipsilateral hemisphere (McKittrick, Lawrence, & Carswell, 2015), gradually increases in both cortex and striatum (Adachi, Itoh, Oishi, & Saeki, 1992). The expression of HA receptors is furthermore modulated (Hu & Chen, 2012), and several lines of evidence have now shown that HA behaves as long-term neuroprotectant on neurological score, cognitive ability, and infarct area reduction after acute ischemia (Liao et al., 2015).

Alterations of the histaminergic transmission are also evident in AD, where the first signs of either increased or decreased HA levels were described in the cortex, basal ganglia, hypothalamus, and hippocampus, together with decreased binding of HA to H1R in the frontal and temporal areas, which correlated with the severity of symptoms. In addition, H3R and HNMT are found to be increased in the prefrontal cortex of patients with AD (Zlomuzica et al., 2016). Remarkably, H3 antagonists ameliorate cognitive deficiencies in AD transgenic mice, also reversing the hyperphosphorylation of tau in the spinal cord and hippocampus (Bardgett, Davis, Schultheis, & Griffith, 2011; Bitner, Markosyan, Nikkel, & Brioni, 2011). Finally, H3 antagonists prevent neuronal death (Fu et al., 2010) and promote neurogenesis (Bernardino et al., 2012), thus suggesting that HA participates in the pathological process of AD and that HA drugs might be therapeutically effective. Not surprisingly, series of Phase-II clinical studies have been carried out to investigate the efficacy and safety of H3R antagonists to treat cognitive symptoms in patients with AD. For instance, GSK239512 is a potent and brain-permeant H3R antagonist in clinical trial for AD (Hu & Chen, 2017).

HD is characterized by motor and nonmotor symptoms for which there is currently no cure. HA signaling is affected in patients with HD (Shan, Dauvilliers, & Siegel, 2015). In particular, HDC, HNMT, H1R, and H3R mRNA levels are increased in the inferior frontal gyrus of patients with HD, showing a positive correlation of HNMT with CAG repeat length, and a negative correlation of HNMT and H1R with age at onset of disease. H2R and H3R are instead decreased in the caudate nucleus of HD patients, and H3R binding is significantly lower in caudate, putamen, and globus pallidus in patients with HD (Van Wamelen et al., 2011). These findings indicate a functional modulation of histaminergic signaling in HD brain and provide a rationale for the use of HA receptor antagonists for therapeutic purposes. Indeed, recent evidence has established that daily administration of a H3R antagonist/inverse agonist improves nonmotor symptoms including strengthening activity rhythms, cognitive performance, and mood in the Q175 mouse model of HD that recapitulates many of the symptoms identified in patients with HD, including disruptions of the sleep/wake cycle (Whittaker, Wang, Loh, Cachope, & Colwell, 2017). These results thus establish that drugs targeting the H3R system may show benefits as cognitive enhancers in the management of HD.

HA is well known to control motor circuits, and motor symptoms such as bradykinesia, tremor and gait impairment are key hallmarks of PD. In particular, the HA system is involved in the basal ganglia neurocircuitry (Bolam & Ellender, 2016) and HA levels and the number of histaminergic fibers are augmented in the substantia nigra, putamen, and globus pallidus of patients with PD. In addition, H3R controlling the synthesis and release of HA is highly expressed in the striatum and forms heterodimers with dopamine D1R and D2R receptors, respectively, inhibiting the second messenger cAMP production and lowering the affinity of dopamine for its receptor. Remarkably, the H3R agonist immepip mitigates the apomorphine-induced turning behavior in 6-hydroxydopamine-lesioned rats, and immepip co-administered with L-DOPA significantly alleviates L-DOPA-induced dyskinesia and chorea. However, direct injection of immepip in the substantia nigra increases the turning behavior following systemic apomorphine administration in rats (Garcia-Galvez et al., 2016). The H3R antagonist thioperamide alleviates apomorphine-induced turning behavior in 6-OHDA-lesioned rats (Nowak et al., 2009) and, finally, the H3R antagonist pitolisant reduces the excessive diurnal sleepiness of patients with PD but without having effects on motor performance (Schwartz, 2011). These are few among the several lines of evidence suggesting that the histaminergic and dopaminergic transmissions are closely linked, although additional studies are needed to fully elucidate the complex role of HA in PD.

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Active HA controls the differentiation of oligodendrocyte precursors, thus playing a central role in the remyelination process occurring after both acute spinal cord lesions, and chronic demyelinating conditions of MS (Chen et al., 2017). HA and its receptors are directly implicated in MS disease pathogenesis, and HA levels are found to be increased in the cerebrospinal fluid of patients with MS. HA plays a critical role in ameliorating MS, by reducing the ability of myelin autoreactive T cells to adhere to inflamed brain vessels, a crucial step in the development of MS. Most recently, a randomized, single-blind, Phase-II clinical study on relapsing-remitting multiple sclerosis has demonstrated the safety, pharmacokinetics, and favorable lesion remyelinating activity of the H3R antagonist/inverse agonist GSK239512 (Schwartzbach et al., 2017). Similarly, in the mouse cuprizone/rapamycin model of demyelination, the systemic administration of the brain-permeable H3R antagonist GSK247246 enhances remyelination and subsequently protects axons (Chen et al., 2017). Finally, the high H3R expression in oligodendroglial cells from patients with MS presenting demyelinating lesions has validated a genetic association between an exonic single nucleotide polymorphism in H3R and the susceptibility to multiple sclerosis (Chen et al., 2017).

Whether released from neurons, microglia, or mast cells, HA participates in CNS diseases also by contributing to vascular changes, alterations in the blood–brain barrier, and modulation of immune functions. The nature of the inflammation, the strength and the resolution of the responses, and more complex events, for instance, the perception of pain during inflammation are also influenced by HA (Bañuelos-Cabrera, Valle-Dorado, Aldana, Orozco-Suárez, & Rocha, 2014).

Overall, these results unequivocally demonstrate that both the levels of HA and the signaling of H1R-H4R in the CNS are strictly controlled and modulated during several pathological conditions and neurological disorders. HA seems to exert protective effects in models of acute and chronic neurodegenerative and neuroinflammatory conditions, to the point that several different HA drugs, in particular H3R modulators, are investigated in recent years for their beneficial effects in animal models of PD, attention-deficit/hyperactivity disorder, schizophrenia, dementia, and depression (Łażewska & Kieć-Kononowicz, 2018; Hu & Chen, 2017). This unanticipated knowledge about the several mechanisms that HA is involved with in the CNS clearly suggests that the field is blooming and that further investigations might even lead to novel uses of the HA therapeutics currently available.

4. A novel histaminergic perspective in ALS

We have described thus far that HA and its receptors are key regulators of a plethora of biological processes and pathological conditions in the CNS. Moreover, the development of transgenic mice lacking HA receptors (Schneider, Neumann, & Seifert, 2014) or unable to synthesize HA (Ohtsu, 2010), in addition to several preclinical studies, have shown clear values for several HA drugs that might find widespread therapeutic applications. Finally, the human variance of HA genes influencing disease susceptibility, severity, and treatment is prospecting even further functions for HA that extend well beyond its established roles. If we now conjugate more than a century of clinical successful investigations in support of HA drugs (Tiligada & Ennis, 2018), with approximately 20 years of failures in ALS clinical trials (Petrov, Mansfield, Moussy, & Hermine, 2017), it appears natural to inquire whether HA might indeed show a true value also in ALS.

Current research goals in ALS include understanding what causes motor neuron death; identifying further genes involved in disease development; validating new biomarkers to aid diagnosis; improving patient stratification and therapy efforts; and discovering new treatments including drugs, antibodies, and stem cell and gene therapies. The aim of this chapter is to introduce a novel histaminergic perspective in ALS by describing how the histaminergic signaling is involved and might even work against the disease (Fig. 1). Given the large, untapped potential for developing always more effective HA drugs, this is surely a promising time for translational HA research in ALS.

4.1. Integrative expression analysis

Recent work has proposed that HA might play a direct role in ALS (Volonté, Parisi, & Apolloni, 2015). First, H1R-H4R, HDC, HNMT, and DAO are abundantly and differently distributed in microglia purified from SOD1-G93A mice (Apolloni et al., 2017), the most exploited animal model that recapitulates key ALS features. HA receptors and enzymes are also expressed in cultured SOD1-G93A primary motor neurons (Apolloni et al., 2019). Moreover, HA receptors and metabolic enzymes are present in glia and motor neurons of lumbar spinal cord of symptomatic SOD1-G93A mice and, most importantly, they are found to be differentially regulated in SOD1-G93A mice during disease progression (Table 2). For instance, H1R is upregulated in the cortex at the symptomatic and the end stage and downregulated in the lumbar spinal cord at the presymptomatic and symptomatic phases. H2R is decreased in the cortex at the symptomatic phase and in the spinal cord at the end stage. H3R seems not to be modulated during disease progression, and H4R is increased in cortex at the presymptomatic phase and in the spinal cord at the symptomatic phase. HDC is significantly overexpressed in the cortex at the symptomatic phase, while it is downregulated in the spinal cord at the presymptomatic phase but upregulated at the end stage of the disease. HNMT is augmented in the cortex and spinal cord at the symptomatic phase. Finally, DAO is not affected during the disease in the cortex but upregulated in the lumbar spinal cord at the symptomatic and the end stage (Apolloni et al., 2017).

In addition to the protein expression data obtained from the SOD1G93A mouse model, whole-genome expression profiles of the motor cortex and spinal cord were obtained from control subjects and patients with sporadic ALS (sALS). Several genes involved in the metabolism, transport, secretion, and signal transduction pathways of HA are indeed confirmed to be differentially deregulated in two separate transcriptome-based subgroups of patients with ALS segregated by unsupervised hierarchical clustering and termed sALS1 and sALS2 (Aronica et al., 2015). In particular, cortical expression of H1R, HDC, HNMT, and DAO is increased in sALS2, while H2R and H3R are selectively reduced. H4R is differently modulated in sALS1 (downregulated) *versus* sALS2 (upregulated), with regard to healthy individuals. On the other hand, spinal cord analysis showed deregulation of H1R (reduced) and H3R (increased) in subgroups sALS1 and sALS2 of patients with ALS (Table 3) (Apolloni et al., 2017). Despite some intrinsic singularities and exceptions, in both subgroups of patients with sALS, the HA system shows substantial upregulation of H1R in the cortex (as in SOD1-G93A mice) but downregulation in the spinal cord (as in presymptomatic and symptomatic ALS mice), together with increased expression of H3R in the spinal cord. Irrespective of the tissue- and disease phase-specific upregulation or downregulation of expression, the pathological implication that stands from these modulations is that the histaminergic system is extensively deregulated in ALS. Interestingly, the overwhelming majority of HA-related genes that emerged as deregulated in SOD1-G93A mice were also found to be deregulated in at least one of sALS patient subgroups (*e.g.*, HRH1 and HNMT), thus offering a rationale for the selection and prioritization of HA genes as potential biomarkers and targets for patient-oriented ALS care (Apolloni et al., 2019).

Recently, a large-scale meta-analysis of genome-wide association studies conducted on 850 patients with sALS within the Chinese population has identified that patients carrying the Ile105 polymorphism on the Thr105Ile allele in the HNMT gene (causing an approximately 60% decrease in HA-degrading enzymatic activity) exhibited a trend toward a delay in symptom onset of approximately three years. This strongly suggests that the Thr105Ile allele in the HNMT gene could potentially be an important therapeutic target and protective modifier for the treatment of ALS (Chen, Kankel, Su, Han, & Ofengeim, 2018). The consequent

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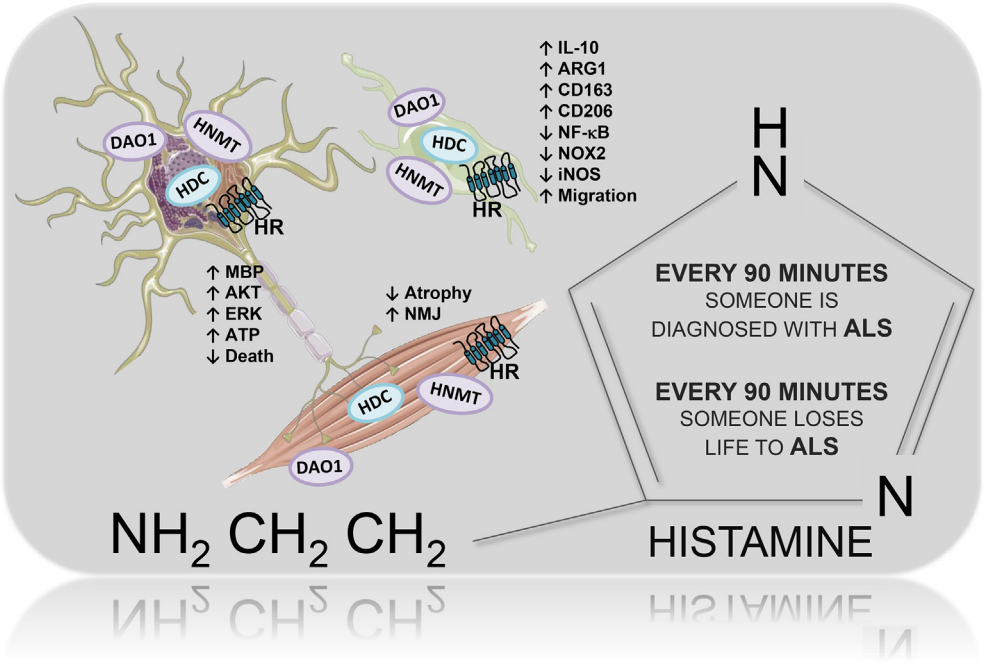

Fig. 1. Histamine targets motor neurons, glial cells, and skeletal muscles in ALS. Schematic representation of the multitarget effects of histamine mainly acting on motor neurons, microglia, and skeletal muscles, all of which express histamine receptors (HR) and enzymes (HDC, HNMT, and DAO1). In motor neurons, histamine activates AKT and ERK1/2 pathways and increases mitochondrial functionality and ATP content, while reducing cell death. In microglia, histamine decreases the pro-inflammatory markers NF-κB, NADPH oxidase 2 (NOX2), and inducible nitric oxide synthase (iNOS) and increases the anti-inflammatory mediators CD206, CD163, arginase1 (ARG1), and interleukin-10 (IL-10), while promoting cell migration. Finally, histamine reduces myelin basic protein (MBP) loss in spinal cord and decreases muscle atrophy and neuromuscular junction (NMJ) denervation. An increased histaminergic signaling after disease onset induces beneficial effects in ALS models.

hypothesis for this correlation is that a beneficial effect might be exerted in patients with ALS by increasing the systemic levels of HA.

To provide a more comprehensive understanding of the HA-related molecular mechanism, further studies have incorporated a multi-omics approach integrating transcriptomic and genomic data with the ALS-linked pathogenic variants from the ALSdb database, thus combining gene expression profiles, copy number variants, and single nucleotide polymorphisms of patients with ALS for capturing HA pathway associations in ALS (Apolloni et al., 2019). Numerous pathological variants are identified in the genes coding for HA receptors and enzymes. In particular, a genome-wide analysis of multiple genomic aberrations occurring in patients with sALS has identified some HA-related genes that are copy number variant-affected (H2R and DAO show amplification, while H3R shows duplication) and that also show a positive correlation with transcriptomic changes in one or both sALS patient subgroups. Among these genes, there are, for instance, genes encoding ADCYAP1, CCKBR, and H3R (Table 4). Moreover, single nucleotide polymorphisms are identified in H1R, H2R, H3R, H4R, HDC, HNMT, and DAO genes. Overall, these results demonstrate that there is a clear homogeneity between the HA-related genes driven by gene expression data, CNV, and SNP, supporting the hypothesis that HA-related genes are candidate driver genes in ALS etiopathogenesis and furthermore establishing that HA is a gene modifier in ALS and a potential therapeutic target.

Table 2
Protein expression of histamine receptors and enzymes in CNS tissues from SOD1-G93A mice during the course of disease.

Target	Presymptomatic	Symptomatic	End stage
	Cortex	*Cortex*	*Cortex*
H1R	=	↑	↑↑
H2R	=	↓↓	=
H3R	=	=	=
H4R	↑	=	=
HDC	=	↑↑	=
HNMT	=	↑	=
DAO	=	=	=
	Spinal cord	*Spinal cord*	*Spinal cord*
H1R	↓↓	↓	=
H2R	=	=	↓↓
H3R	↓↓	=	=
H4R	=	↑↑	=
HDC	↓↓	=	↑↑
HNMT	=	↑↑	=
DAO	=	↑↑	↑

Protein expression data from cortex and spinal cord of SOD1-G93A mice at different disease stages are shown as fold change values with regard to wild type (Apolloni et al., 2019); (Apolloni et al., 2017). One arrow: 0 < value<2; Two arrows: 2 ≤ value≤4.

Table 3
Transcription expression of histamine receptors and enzymes in CNS tissues from sporadic ALS patient subgroups.

Target	sALS1	sALS2
	Cortex	*Cortex*
H1R	↑↑	↑↑
H2R	=	↓
H3R	=	↓↓
H4R	↓	↑↑
HDC	=	↑
HNMT	=	↑↑
DAO	=	↑↑
	Spinal cord	*Spinal cord*
H1R	↓	↓↓
H2R	=	=
H3R	↑↑	↑↑
H4R	=	=
HDC	=	=
HNMT	=	↑
DAO	=	=

Transcription data of histamine-related genes in post-mortem cortex and spinal cord of sporadic ALS patient subgroups are indicated as fold change values with regard to those of healthy individuals (Apolloni et al., 2019); (Apolloni et al., 2017). One arrow: 0 < value<2; Two arrows: 2 ≤ value≤4.

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Table 4
Genetic and transcription variations of main histamine-related genes in sporadic ALS patients.

Target	CNV	SNP	Transcripts
H1R	—	✓	✓
H2R	✓	✓	—
H3R	✓	✓	✓
H4R	—	✓	—
HDC	—	✓	—
HNMT	—	✓	✓
DAO	✓	✓	—
ADCYAP1	✓	✓	✓
CCKBR	✓	—	✓

Data are reported from Apolloni et al. (2019). CNV: copy number variations, SNP: single nucleotide polymorphisms. Transcript data are reported from autoptic spinal cord tissue.

4.2. From macrophage/microglia involvement to disease progression

The contribution of inflammation to neurodegenerative diseases is increasingly recognized, but the role of inflammation in ALS is not totally understood. In ALS spinal cord and cortex, inflammation is sustained by innate immune responses mediated by inflammatory macrophages/microglia and mast cells and, moreover by adaptive immune responses sustained by T cells. ALS spinal cord presents dense macrophage infiltration involving both white and gray matter, with the heaviest infiltration at lateral and ventral columns. Abundant macrophages surround and phagocytize neurons that appear to be dying in the gray matter. ALS spinal cords are also sparsely infiltrated with HA-releasing mast cells (Graves et al., 2004). A recent report has shown that degranulating mast cells are also abundant in the autopsied quadriceps muscles from patients with ALS but not in healthy individuals. Further, mast cells and neutrophils (producing and releasing HA) are found associated with myofibers and motor endplates and are particularly abundant around motor axons in the extensor digitorum longus muscle, sciatic nerve, and ventral roots of spinal nerves in symptomatic SOD1-G93A rats, indicating that immune-macrophage-microglia-mast cell infiltration extends along the entire peripheral motor pathway in ALS (Trias et al., 2017; Trias et al., 2018).

Activation of microglia is a complex event that can induce a gradual conversion into numerous different phenotypes, each resembling a specific inflammatory state. During ALS pathogenesis, microglial cells proliferate and switch their phenotype from the protective anti-inflammatory type to the neurotoxic pro-inflammatory type. By confirming results that are already reported in naïve cells (Ferreira et al., 2012), in SOD1-G93A microglia, HA directly affects cell migration *in vitro* (Apolloni et al., 2017). Moreover, HA transiently activates the MAPK pathway and stimulates anti-inflammatory mediators such as interleukin-6, interleukin-10, arginase 1, CD163, CD206, and purinergic P2Y12 receptor. In parallel, HA reduces pro-inflammatory pNF-κB and NADPH oxidase 2 (Apolloni et al., 2017). Thus, HA seems very effective in reverting the pro-inflammatory phenotype of SOD1-G93A microglia while boosting its anti-inflammatory capacity, as thoroughly described in other neurodegenerative conditions (W. Hu & Chen, 2017). On the other hand, analysis in nontransgenic naïve microglia confirms that HA stimulates a pro-inflammatory phenotype (Apolloni et al., 2017), in line with what was previously established (Dong et al., 2014; Ferreira et al., 2012; Frick et al., 2016; Rocha et al., 2016; Rocha, Pires, Esteves, Graça, & Bernardino, 2014). This reinforces the notion that the inflammatory context of the environment is fundamental for driving the microglia response to HA (Barata-Antunes et al., 2017).

Remarkably, this is demonstrated in part also *in vivo*, after an acute single injection of the brain-penetrant HA precursor histidine in SOD1-G93A mice at the symptomatic phase of the disease, that is, within an overt inflammatory context. A potentiated HA transmission sustained by histidine indeed increases the protein expression of anti-inflammatory arginase 1; further, it decreases the number of Iba1- and CD68-positive microglia/macrophages and the pro-inflammatory NADPH oxidase 2 and NF-κB proteins in the lumbar spinal cord (Apolloni et al., 2017). Most strikingly, chronic administrations of scaling doses of histidine to SOD1-G93A mice from the insurgence of the first symptoms until the end stage of the disease produce overall beneficial effects. In particular, histidine ameliorates behavioral features of ALS, delays disease progression, improves motor performance, increases life span, attenuates motor neuron loss and neuroinflammation in the spinal cord, and finally improves neuromuscular junction integrity and muscle atrophy (Apolloni et al., 2019). This confirms that histidine/HA acts not only as a peripheral immunomodulatory transmitter but also as a central neuroprotective agent. Of note, these results are in accordance with data showing that HA protects skeletal muscles against exercise-induced fatigue (Niijima-Yaoita et al., 2012), and HA therapy increases tetanic forces of myoblasts, reduces muscle injury, and improves motor performance in Duchenne muscular dystrophy in mice (Gurel et al., 2015).

The fact that histaminergic molecules might possess a broad bioactivity in ALS models was in part anticipated by previous results. Chronic administration of a brain-penetrant antihistamine compound with well-known immune-modulating properties, clemastine, in fact slightly delayed disease progression and mildly extended survival of SOD1-G93A mice but when administered only before the insurgence of the first symptoms and up to the early symptomatic phase (*i.e.*, from postnatal day 40 to postnatal day 120). Under these conditions, clemastine induces a strong anti-inflammatory phenotype in the spinal cord, reduces SOD1 aggregates, and modulates autophagy, thus suggesting that modulation of autophagy could be indeed a promising therapeutic strategy in ALS (Apolloni, Fabbrizio, Amadio, & Volonté, 2016). Moreover, low clemastine doses enhance motor neuron survival and increase anti-inflammatory Arginase-1 protein and BDNF mRNA expression, while inhibiting the protein levels of CD68, P2X7R, phospho-ERK1/2, and the NADPH oxidase 2 in the lumbar spinal cord of SOD1-G93A mice at the end stage of the disease (Apolloni, Fabbrizio, Parisi, Amadio, & Volonté, 2016). These studies suggest that some beneficial actions of clemastine are demonstrated only in the presymptomatic/early symptomatic phase. This confirms a critical and very narrow window of efficacy for the use of histaminergic compounds in ALS (Coughlan, Mitchem, Hogg, & Prehn, 2015) as previously demonstrated also in the partial sciatic nerve ligation model of neuropathic pain (Yu et al., 2016). Without doubt, the clemastine therapeutic regimen highly restrains the potential clinical testing of such drugs. Conversely, the more durable and robust beneficial effects gained by the histaminergic treatment during the symptomatic phase of the disease surely establish a broader translational impact of HA signaling in ALS, also confirming the existence of an optimum lag for histaminergic drug delivery.

By discussing the extent of the histaminergic modulation in ALS within distinct timeframes and biological actions, evidence stands that both HA and anti-HA strategies do interfere with ALS pathogenesis. This confirms the dual role played by HA compounds that generally possess beneficial properties within a pathologic environment (during disease progression) but that elicit detrimental actions within a physiological milieu (before symptom onset). Indeed, during the symptomatic phase of ALS, when disease progression accelerates in SOD1-G93A mice in the presence of M1-like detrimental inflammatory microglia, HA becomes anti-inflammatory and neuroprotective and it improves pathology and survival of ALS mice. Conversely, under presymptomatic conditions exhibiting M2-like microglia functions that are beneficial for motor neurons, an anti-histaminergic therapy seems to work, although to a lesser extent. This histaminergic/anti-histaminergic dichotomy might be easily explained by HA drugs acting on molecular and cellular paradigms that possess dual roles in the disease. Of note, this mirrors a dichotomy previously demonstrated, for instance, in ALS microglia, acting either beneficially to prevent disease progression at early stages or detrimentally to support disease progression through the spinal cord at later stages. A similar dualism is overall generalized in ALS, if we look for instance at early protective T2 immune

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phases *versus* late pathogenic T1 phases (Beers, Zhao, & Appel, 2018), at the stage-specific neuroimmunological response induced by NF-κB activation in astrocytes (Ouali Alami et al., 2018), at the early stimulation or late inhibition of the inflammatory purinergic P2X7 receptor (Apolloni et al., 2013; Apolloni et al., 2014), early or late stage autophagy (Yuan, Zhang, & Li, 2017), and early cortical hyperexcitability and late hypoexcitability (Geevasinga, Menon, Özdinler, Kiernan, & Vucic, 2016; Martínez-Silva et al., 2018).

Irrespective of the use of histaminergic *versus* antihistaminergic compounds, the possibility of elucidating the time gap over which a pharmacological strategy might be successful is crucial for understanding the timeframe over which motor neuron degeneration can be prevented. It is still debated if ALS begins suddenly within a background of a healthy nervous system, with drastic loss of motor neurons and emergence of progressive weakness or, instead, with slow attrition of motor neurons and compensatory mechanisms temporarily delaying symptoms and irreversibly evolving, once the degenerative process overcomes the compensatory mechanisms. What is surely undeniable is that ALS remains a challenging mission because of the complexity of its genetic architecture, the aggravating incidence of environmental factors, and the multifactorial nature of its biological and molecular mechanisms.

Single modality of the "one-molecule-one-target" strategy for treating ALS has failed thus far, and future therapies on the "combination-drugs-multi-targets" approach will need to address multiple aspects to halt the progression of the disease. Recent works indeed outline a transformative approach for studying and treating complex and heterogeneous diseases such as ALS, and the last years have seen important steps toward the development of viable diagnostic and prognostic markers for ALS progression (Taga & Maragakis, 2018). Under this perspective, this review provides a new understanding of HA-related molecular mechanisms that might contribute to the disease. Overall, we have disclosed a novel important role for HA in the characterization of the complex multi-gene network and molecular pathways responsible for ALS and demonstrated a favorable treatment logistic and potential translational impact of HA in the development of more effective therapeutics. Supported by recent experimental evidence, we have also proposed that HA might be a gene modifier of the disease, thus establishing a novel mean for affecting ALS variability. By stimulating a further assessment of HA drugs, we hope to provide a new insightful approach to the research on ALS and to open a new window for ALS clinical trials. The indication that HA might be comprised within the multidrug strategies or broad-spectrum molecules to be adopted to understand and alleviate ALS is certainly intriguing and encouraging.

5. Concluding remarks

The incidence of ALS globally and the number of cases will increase from approximately 223,000 as estimated in 2015 to a projected approximate of 377,000 by 2040, representing an increase of 69% (Arthur et al., 2016). Because this figure shows no signs of abating, predominantly due to aging of the population, especially among developing nations, one of the greatest challenges for ALS treatment is thus to decipher the enormous complexity and heterogeneity – in origin, mechanism, and clinical expression – that this debilitating disease is characterized by. However, ALS poses strong, sometimes daunting challenges for understanding its mechanisms and developing effective treatments to the point that several pharmacological approaches showing promise against ALS have not reached sufficient efficacy and safety *in vivo* to support their continuation into human clinical trials.

Here we have endorsed the novel concept that histaminergic modulation might work against ALS. We have referred that HA-related genes are dysregulated in the cortex and spinal cord from patients with sporadic ALS, as well as in SOD1-G93A mice as a function of disease progression, and finally in ALS microglia and motor neuron cultures. Moreover, we have reported that an integrative multi-omics approach combining gene expression profiles, copy number variants, and single nucleotide polymorphisms of patients with ALS has captured HA pathway associations in ALS, thus providing a comprehensive understanding of HA-related molecular mechanisms that might contribute to the disease. Most importantly, we have discussed very recent works on the direct anti-inflammatory and neuroprotective action of HA compounds, not only *in vitro* but most of all *in vivo* in SOD1-G93A mice, by highlighting some durable and robust beneficial effects gained by an histaminergic treatment started at the symptomatic phase of the disease.

Actually, the HA system is not new as a drug target in several animal models of diseases and proposed to display a clear value for a wide range of clinical conditions in the CNS (for a comprehensive review, consult Hu & Chen, 2017). HA drugs display beneficial effects in animal models of Parkinson's disease, dementia, and depression and are already in clinical trials for Alzheimer's disease, drug abuse, sleep disorders, and relapsing-remitting multiple sclerosis. In particular, one of the most examined H3R ligands, pitolisant (Wakix®) (Schwartz, 2011), is currently in Phase-III clinical trials for drug abuse and sleep disorders and is approved by the European Medicines Agency for narcolepsy (Romigi, Vitrani, Lo Giudice, Centonze, & Franco, 2018).

Although we are aware that much has still to be learned about the therapeutic strategies possibly halting or treating ALS, in this review, an attempt has been made to challenge the histaminergic signaling as a candidate mechanism in the disease. We trust that HA will contribute to expand our knowledge about ALS and that a valuable HA therapy will be further verified in ALS. Because of its pleiotropic function, we estimate that the future of HA research is still unpredictable but without doubt exciting. HA looks far beyond to effecting just allergy, it might be that broad-spectrum compound deserving a renewed and far-reaching momentum in ALS.

Declarations of Competing Interest

The authors declare that there are no conflicts of interest.

The work has been approved by all authors.

The manuscript has not been published and is not under consideration for publication elsewhere.

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