

## Histamine: The Missing Link in the Pathogenesis of Some Brain Disorders

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### Historical Background

Histamine (HA) is a rebellious neurotransmitter with pleiotropic activity. Among the classics (adrenaline, noradrenaline, acetylcholine, serotonin), HA has been the last to reach a status of recognition as a neurotransmitter with defined neuromodulatory functions. According to data obtained from the PubMed database, during the period 1918-2016, 83,801 papers on HA have been published (134,040 papers on adrenaline (1914-2016); 116,182 papers on noradrenaline (1946-2016); 131,361 papers on serotonin (1946-2016); and 86,369 papers on acetylcholine (1934-2016). These numbers reflect the weak consideration of the scientific community with respect to HA as compared with the other classical neurotransmitters.

HA ( $\beta$ -aminoethylimidazole) was synthesized by Windaus and Vogt in 1907. In 1910, Dale and Laidlaw discovered the role of HA in anaphylactic shock; in 1927, Best and co-workers found HA (also known at that time as Lewis' Substance H) in several tissues. Between 1948 and 1955, Folkow and Furghott postulated the existence of two different HA receptors. In 1966, Ash and Schild identified HA H1 receptors, and in 1972 Black and colleagues did the same with H2 receptors. In 1955, Pepys postulated that HA could affect immune response. For one decade (1955-1965) the interest in HA was focused on allergy, bronco-pulmonary function, and gastric secretion (Sir James White Black was awarded the Nobel Prize for Medicine in 1988 for work leading to the development of cimetidine). In the early 1960's, Carlini and Green studied the subcellular distribution of HA in the brain, and in 1973 Baudry and co-workers studied the distribution of histidine decarboxylase in neural tissue. It was in 1970 when Douglas and Green proposed that HA was a neurotransmitter, and the idea was validated by Snyder and Taylor in 1972, by Browstein in 1974, and by Schwartz in 1975. This was the beginning of a new era in HA research, and several groups started an exciting race to map HA in the brain [1]. In 1982, Wilcox and Seybold demonstrated the presence of intraneuronal HA using anti-HA antibodies; in 1982-1984, Wada's and Watanabe's group in Japan generated specific histidine decarboxylase antibodies [2] and were able, together with Tohyama's group at Osaka University Medical School, to map brain HA using histidine decarboxylase as a marker [3,4]. At the same time, Steinbusch and Mulder in The Netherlands [5] and Panula et al. [6], in the USA, also mapped HA in the posterior hypothalamus by using specific anti-HA antibodies [1]. Since then, brain HA became a fashion for a decade and thereafter brain HA research declined again to a non-enthusiastic level. In 1985, Ganellin and Schwartz [7] published a book, as a tribute to Heinz Schild, with contributions from the most relevant authors of the time, including Haas, Pollard, Hough, Arrang, Saeki, Green, Weinreich, Watanabe, and Richelson [7]. Another important volume was published by Watanabe and Wada in 1991 with chapters by Fukui, Yamatodani, Schwartz, Tohyama, Panula, Steinbusch, Nagy, Tuomisto, Haas, Green, Kupfermann, Cacabelos, Richelson, Sakata, Takeda,

Philippu, Saeki, Nowak, Wada and Watanabe, reporting the most relevant findings in brain HA function [8].

### Brain Histamine

HA is in a privileged position to display multiple pleiotropic functions in peripheral tissues and in the CNS. HA is synthesized by histidine decarboxylase (HDC; EC 4.1.1.22) from L-histidine in different cellular compartments (mast cells, basophils, glial cells, endothelial cells, neurons). HA is metabolized by histamine N-methyltransferase (HNMT) which inactivates HA, transferring a methyl group from S-adenosyl-L-methionine to HA. HA acts through different types of HA receptors (H1R, H2R, H3R, H4R). H1R and H2R are widely distributed in most cells and tissues; however, H3Rs are mainly expressed in the CNS, and H4Rs are expressed in hematopoietic cells, indicating their function in neurotransmission and immunomodulation, respectively. H3R is a recognized drug target for neuronal diseases, such as cognitive impairment, schizophrenia, sleep/wake disorders, epilepsy and neuropathic pain [9]. The presence of H4Rs in the CNS is still a controversial matter [10,11].

The organization of the brain histaminergic system shows a strategic disposition, with HA neurons located in the posterior hypothalamus, from where ascending pathways (to the anterior hypothalamus, limbic structures (hippocampus), neocortex, and subcortical structures) and descending pathways (to the brain stem and spinal cord) are organized [3-6]. Recent studies by Moriwaki et al. [12] distinguish five neuronal clusters (E1-E5) in the hypothalamus at the postnatal stage. Neuronal HA clusters are localized in the ventrolateral part of the most posterior hypothalamus (E1), ventrolateral part of the posterior hypothalamus (E2), ventromedial part from the medial to the posterior hypothalamus (E3), periventricular part from the anterior to the medial hypothalamus (E4), and diffusely extended part of the more dorsal and almost entire hypothalamus (E5).

### Mast Cells

Brain HA is distributed in several compartments (neuronal, glial, endothelial, mast cells). Mast cells are connective tissue cells, discovered by Ehrlich in 1887, which are rich in metachromatic granules containing HA, heparin and serotonin. Riley, West and coworkers were the first to establish an association between mast cells and HA in 1953, and Benditt and colleagues showed, in 1955, that mast cells also contained 5-hydroxytryptamine (5-HT; serotonin). In 1953, Riley demonstrated that injection of HA releasers was followed by damage to mast cells. Examples of HA releasers include compound 48/80, mast cell-degranulating peptide (MCD), polylysine, polymyxin B, dextran, phosphatidylserine, mellitin, F-Met-tripeptides, C5a/C3a anaphylotoxins, C4a, calcium ionophore A23187, and many cytokines and growth factors. Many, if not all, mast cells are innervated by varicose axons in different body structures, and even an "axon reflex"

pathway involving mast cells was proposed in the skin by Kiernan in 1965 [13]. Mast cell secretory granules contain a great variety of mediators, such as histamine, serotonin, tryptase, chymase, and antizyme inhibitor 2 (AZIN2), an activator of polyamine biosynthesis whose catalyzing enzyme is ornithine decarboxylase [14]. Mast cells are resident in the brain and contain numerous mediators, including neurotransmitters, cytokines, and chemokines, that are released in response to a variety of natural and pharmacological triggers. Brain mast cells are of two types, namely, metachromatic type I cells and normochromatic type II cells, or neurolipomastocytoid cells. In mice devoid of mast cells (*W/W<sup>v</sup>* mice), the administration of  $\alpha$ -fluoromethylhistidine (FMH), a suicide inhibitor of HDC, reduces the concentration of brain HA to nearly zero, suggesting that approximately 50% of the content of HA in the CNS belongs to the non-neuronal pool [15,16]. The presence of mast cells in meninges and perivascular locations on the brain side of the BBB, especially in thalamic and hippocampal regions, may indicate that this cell type is relevant in neurovascular responses. The number of mast cells in the brain fluctuates with stress and various behavioral and endocrine states. Mast cells migrate to critical regions influencing neuronal activity, repairing tissue damage or aggravating inflammatory processes within the CNS. These properties suggest that mast cells are poised to influence neural systems underlying behavior. Using genetic and pharmacological loss-of-function models, Nautiyal et al. [17] performed a behavioral screen for arousal responses including emotionality, locomotor, and sensory components and found that mast cell-deficient *Kit<sup>W-sh/W-sh</sup>* (*sash<sup>-/-</sup>*) mice had a greater anxiety-like phenotype than WT and heterozygote littermate control animals in the open field arena and elevated plus maze. Blockade of brain, but not peripheral, mast cell activation increased anxiety-like behavior. Brain mast cells might be implicated in the modulation of anxiety-like behavior and provide evidence for the behavioral importance of neuroimmune links [17].

## Microglia

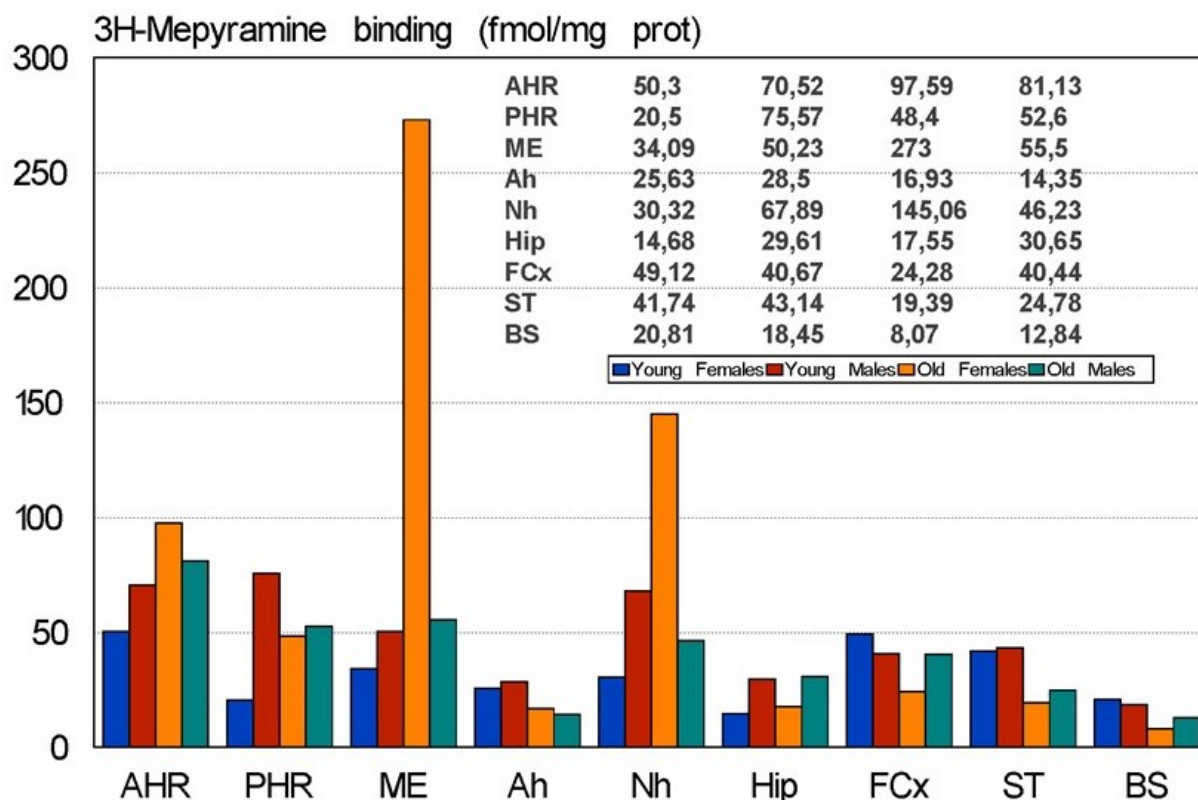
Microglia can constitutively express HA receptors (H1R, H2R, H3R, H4R), and the expression of H1R and H4R can be selectively upregulated by HA in microglial cells in a dose-dependent manner. HA can also stimulate microglia activation and production of proinflammatory cytokines. HA induces TNF- $\alpha$  and IL-6 release from activated microglia via H1R and H4R-MAPK and the PI3K/AKT-NF-kappa B signaling pathway [18]. Microglia express H2R, H3R, histidine decarboxylase, and histamine N-methyltransferase. Both forskolin-induced cAMP accumulation and ATP-induced intracellular  $Ca^{2+}$  transients are reduced by the H3R agonist imetit but not by the H2R agonist amthamine. H3Rs can regulate various microglial functions. HA and imetit inhibit microglial chemotaxis, phagocytosis, and lipopolysaccharide (LPS)-induced cytokine production [19]. HA and substance P can trigger microglial activation and release of pro-inflammatory factors from microglia, thus contributing to the development of microglia-mediated inflammation in the brain [20].

## Brain Functions

The interplay of brain HA in neurons, endothelial cells, glia, and mast cells is fundamental for the regulation of diverse physiological functions (neuroendocrine system, circadian rhythms, sleep-wakefulness cycle, psychomotor activity, mood, learning, cognition, appetite and eating behavior); and alterations in multicompartment brain HA are involved in several pathological conditions [21-24].

HA is implicated in the control of arousal state, exerting a potent phase-shifting effect on the circadian clock in the suprachiasmatic nucleus (SCN). To reset the circadian clock, HA increases  $[Ca^{2+}]_i$  in SCN neurons by activating CaV 1.3 channels through H1Rs, and secondarily by causing  $Ca^{2+}$ -induced  $Ca^{2+}$  release from RyR-mediated internal stores [25]. Light has direct effects on sleep and wakefulness causing arousal in diurnal animals and sleep in nocturnal animals. Histaminergic neurotransmission attenuates the light-induced sleep response during the dark period [26]. Using knockout (KO) mice lacking HDC, Parmentier et al. [27] demonstrated the importance of histaminergic neurons in maintaining wakefulness under behavioral challenges. H1-receptor KO (*H1<sup>-/-</sup>*) mice share several characteristics with HDC KO mice, including a decrease in wakefulness after lights-off despite its normal baseline daily amount, a decreased EEG slow wave sleep (SWS)/W power ratio, and inability to maintain wakefulness in response to behavioral challenges. Most of these effects are mediated by central H1Rs [27]. Yu et al. [28] reported that GABA and HA are involved in the mechanisms of wakefulness. HA neurons in the tuberomammillary nucleus (TMN) of the hypothalamus form a widely projecting, wake-active network that sustains arousal. HA neurons contain GABA. Selective siRNA knockdown of the vesicular GABA transporter (*vgat*, *SLC32A1*) in HA neurons produces hyperactive mice with an exceptional amount of sustained wakefulness. Ablation of the *vgat* gene throughout the TMN further sharpens this phenotype. Optogenetic stimulation in the caudate-putamen and neocortex of HA axonal projections from the TMN evokes tonic, extrasynaptic GABA<sub>A</sub> receptor Cl<sup>-</sup> currents onto medium spiny neurons and pyramidal neurons. These currents are abolished following *vgat* gene removal from the TMN area. Thus, wake-active HA neurons may generate a paracrine GABAergic signal that serves to provide a brake on over activation of HA, and to increase the precision of neocortical processing. Yu et al. [29] studied the contribution of one putative local clock in mouse histaminergic neurons in the tuberomammillary nucleus to the regulation of the sleep-wake cycle. Histaminergic neurons are silent during sleep, and start firing after wake onset. HA enhances wakefulness. HDC gene expression varies with time of day. Deletion of the *Bmal1* (*Arntl/Mop3*) clock gene from HA cells removes this variation, producing higher HDC expression and brain HA levels during the day. The consequences include more fragmented sleep, prolonged wakefulness at night, shallower sleep depth (lower nonrapid eye movement [NREM]  $\delta$  power), increased NREM-to-REM transitions, hindered recovery sleep after sleep deprivation, and impaired memory. Removing *BMAL1* from histaminergic neurons does not, however, affect circadian rhythms.

There are important age- and sex-related changes in the concentration of HA and H1Rs in different regions of the CNS [30] (Figure 1). Dramatic changes in HA and H1Rs have been reported after surgical manipulation of the neuroendocrine system (e.g. castration, adrenalectomy), clearly indicating the relevant effect that changes in the hypothalamic-pituitary-gonadal axis and hypothalamic-pituitary-adrenergic axis exert on brain HA [15,30]. Similarly, direct interactions between the somatotropinergic system (GRH/SS-GH-IGF1) and HA [31] and the vasopressinergic system and HA have been extensively demonstrated [32]. Interaction of HA with dopamine, noradrenaline, serotonin and other neurotransmitters may contribute to the regulation of different neuroendocrine functions [33].



**Figure 1:** Age- and sex-related changes in brain histamine H1 receptors. AHR: Anterior hypothalamic region; PHR: Posterior hypothalamic region; ME: Median eminence; Ah: Adenohypophysis; Nh: Neurohypophysis; Hip: Hippocampus; FCx: Frontal cortex; ST: Striatum; BS: Brain stem.

HA is a powerful regulator of neuroimmune function [13]. L-Histidine and HA induce a time- and dose-dependent decrease in hypothalamic IL-1 $\beta$ , and this effect is not affected by mepyramine (H1R antagonist), famotidine (H2R antagonist) or thioperamide (H3R antagonist) [34]. The abolishment of neuronal HA by  $\alpha$ -fluoromethylhistidine, a suicide inhibitor of HDC, causes a significant decrease in the hypothalamic concentration of TNF- $\alpha$  [35].

### Brain Pathology

Important changes in the peripheral and central levels of HA occur in patients with different CNS disorders. HA has been studied in anxiety, depression, psychosis, stroke, dementia (Alzheimer's disease, vascular dementia), Parkinson's disease, attention-deficit/hyperactivity disorder, migraine, sleep disorders, epilepsy, mental retardation, cerebrovascular encephalopathy, multiple sclerosis, brain tumors, cranial nerve neuropathies, and post-traumatic brain injury [22,36]. Although the peripheral levels of HA exhibit a great variability, high levels of HA are currently seen in cases with psychosis, stroke, attention-deficit/hyperactivity disorder, Parkinson's disease, and brain tumors; however, HA changes tend to be genotype-related and the quantification of peripheral HA in individual cases is of poor value, except in those patients with a clear immunologic/allergic condition [36].

Altered HA neurotransmission has been reported in an animal model of Lesch-Nyhan syndrome, an X-linked chromosomal disorder with congenital deficiency of hypoxanthine-guanine phosphoribosyltransferase. These animals show a decrease in dopamine and 3-methoxytyramine concentrations in the brain, together with reduced 1-methylhistamine and 1-methylimidazole-4-acetic acid concentrations in the brain and medulla [37]. Heidari et al. [38] identified two homozygous HNMT alterations, p.Gly60Asp and p.Leu208Pro, in patients affected with nonsyndromic autosomal recessive intellectual disability from two unrelated consanguineous families of Turkish and Kurdish ancestry, respectively. p.Gly60Asp disrupts the enzymatic activity of the protein, and p.Leu208Pro reduces protein stability, resulting in decreased HA inactivation.

Brain HA alterations have also been reported in other CNS and neurometabolic disorders such as anxiety [39], amyotrophic lateral sclerosis [40], multiple sclerosis [41], Parkinson's disease [42], L-DOPA-induced dyskinesia [43], migraine [44], psychosis [42], Tourette syndrome [45,46], attention-deficit/hyperactivity disorder [47], narcolepsy [48], eating disorders, obesity and metabolic syndrome [49]. Severe head trauma is associated with a marked loss (41%) of HA neurons. Reduced histamine signaling may contribute to increased sleep need, and therapies that enhance histaminergic tone may improve arousal after head trauma or other conditions [50]. Furthermore, HA H1 antagonists have hypnotic, appetite-promoting, and sedative side effects, and second-generation antipsychotics



(olanzapine, quetiapine) have potent antagonistic effects on H1Rs [51]. Studies in animal models (HDC-deficient mice,  $\alpha$ -FMH-treated mice) show that selective serotonin reuptake inhibitors require the integrity of the brain histamine system to display their pharmacodynamic effects [52]. Results of clinical trials with H3 antagonists such as ABT-288 [53] or GSK239512 have recently been reported in dementia [54]. GSK239512, a brain-penetrant H3R antagonist, was also investigated as a potential cognitive enhancer in patients with schizophrenia [55]. However, no breakthroughs have been achieved with novel antihistaminics in brain disorders.

H3Rs are expressed in various tumors and correlated with malignancy and tumor proliferation. H3R mRNA and protein levels are up-regulated in glioblastoma (GBM) and glioma cell lines

compared to normal brain tissue and astrocytes. In the U87MG cell line, inhibition of H3R by siRNA or the antagonist ciproxifan suppresses proliferation, invasiveness, and the expression of epithelial-mesenchymal transition (EMT) activators. Inhibition of H3R by siRNA or ciproxifan inactivates the PI3K/Akt and MEK/ERK signaling pathways, while inhibition of Akt or ERK activity with antagonists or siRNAs suppresses H3R agonist (R)- $\alpha$ -(-)-methylhistamine dihydrobromide-mediated invasion and reorganization of cadherin-household. These data reported by Lin et al. [56] suggest that overexpression of H3Rs is associated with glioma progression and that inhibition of H3Rs leads to suppressed invasion and EMT of GBM by inactivating the PI3K/Akt and MEK/ERK pathways in gliomas.

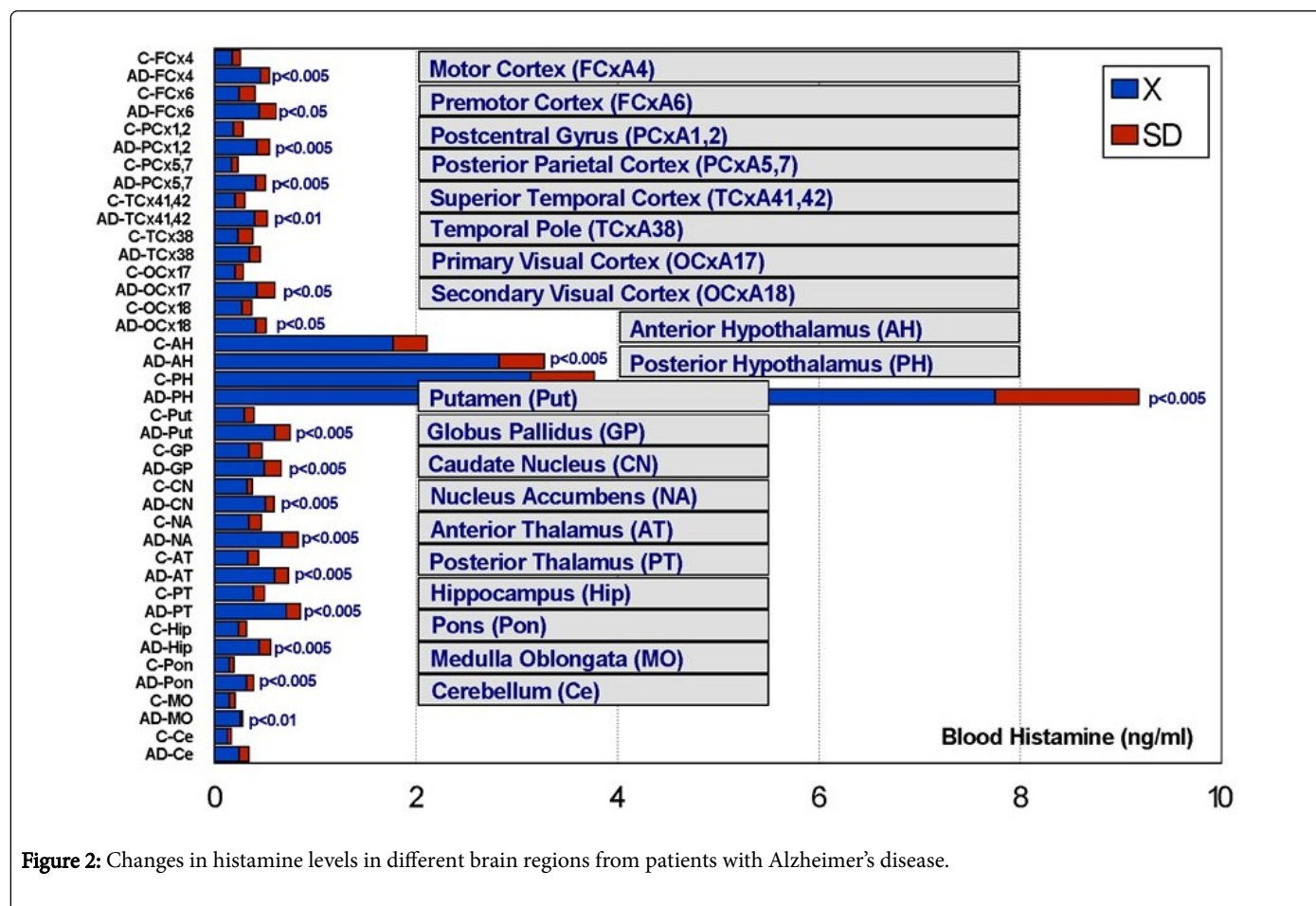


Figure 2: Changes in histamine levels in different brain regions from patients with Alzheimer's disease.

### Alzheimer's disease

In 1991, a profound histaminergic dysregulation was observed in patients with Alzheimer's disease (AD), where HA levels are significantly increased in most CNS regions [57] (Figure 2). HA, TNF- $\alpha$  and IL-1 $\beta$  regulate each other in the hypothalamus. Changes in HA, TNF- $\alpha$  [58], and IL-1 $\beta$  [58,59] in AD correlate with cerebrovascular dysfunction and cognitive decline [21,60]. Furthermore, improvement in cognitive function with neuroprotectants (e.g. CDL-choline) [61-63] or vegetal neurotrophins (e.g. anapsos) [64,65] can reverse alterations in HA, TNF- $\alpha$  and IL-1 $\beta$  levels in AD and in animal models of dementia [13,34,64-67]. AD-related neurodegeneration exhibits a pathological phenotype compatible with a reactive neuroinflammatory process in which HA, TNF- $\alpha$  and IL-1 $\beta$ , among many other immune

effectors, are involved. There is also a correlation between microglia activation and APOE genotypes [68,69]; and peripheral HA levels are also APOE-related, with the lowest levels present in patients harboring the APOE-4 allele [70] (Figure 3). An association between APOE-4 and increased expression of CD95 on T cells has also been reported, suggesting that hyperexpression of Fas mRNA and surface Fas receptor on CD45RO<sup>+</sup> T lymphocytes may explain the occurrence of inflammatory cellular infiltrates in AD brain tissue [71]. Recent data also indicate that mast cells are close to amyloid plaques in AD. Mast cells drastically accumulate in cortical and hippocampal regions prior to the consolidation of amyloid plaques in brain slices of APP<sup>swe</sup>/PS1<sup>dE9</sup> mice, a murine model of AD. This may explain the high levels of HA found in AD brains, probably indicating that mast cells act as

early sensors of amyloid peptide and recruit other cells to the neuroinflammatory response, thus playing a critical role in the onset and progression of AD [72-74].

This brief summary on brain HA data illustrates the potential role of HA as a fundamental player in AD-related neuroinflammation and in other neuropsychiatric disorders [24,36].

### Neuroimmunology

Over the past 30 years, growing evidence has revealed the dense interplay of neurotransmitters, neuropeptides, hormones, and immune effectors in the regulation of complex behaviors. Since the pioneering work of George Freeman Solomon, and the excellent synopses of papers collected by Cotman et al. [75], Goetzl and Spector [76], Ader et al. [77], Baxter and Ross [78], Husband [79], and Thèze [80], among many others, abundant literature in the field reflects the potential role

of particular neuroimmune events in the pathogenesis and phenotypic expression of complex disorders of the CNS [36].

Diverse data provide support to a multidimensional crosstalk among neural, endocrine, and immune signals probably contributing to global homeostasis, constant surveillance to maintain control against exogenous and/or endogenous stressors, brain maturation and development, neuroprotection, and fine-tuning of brain functions associated with higher activities of the CNS. Neuroimmune dysfunction may be part of the pathogenesis of different CNS disorders, including mental disorders (schizophrenia, depression, anxiety, post-traumatic stress disorder), neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Prion disease), brain infections, stroke, brain tumors, and demyelinating disorders. It is likely that the neuroimmune system acts as a regulatory, defense system which reacts against noxious stimuli that endanger brain function stability and optimum performance.

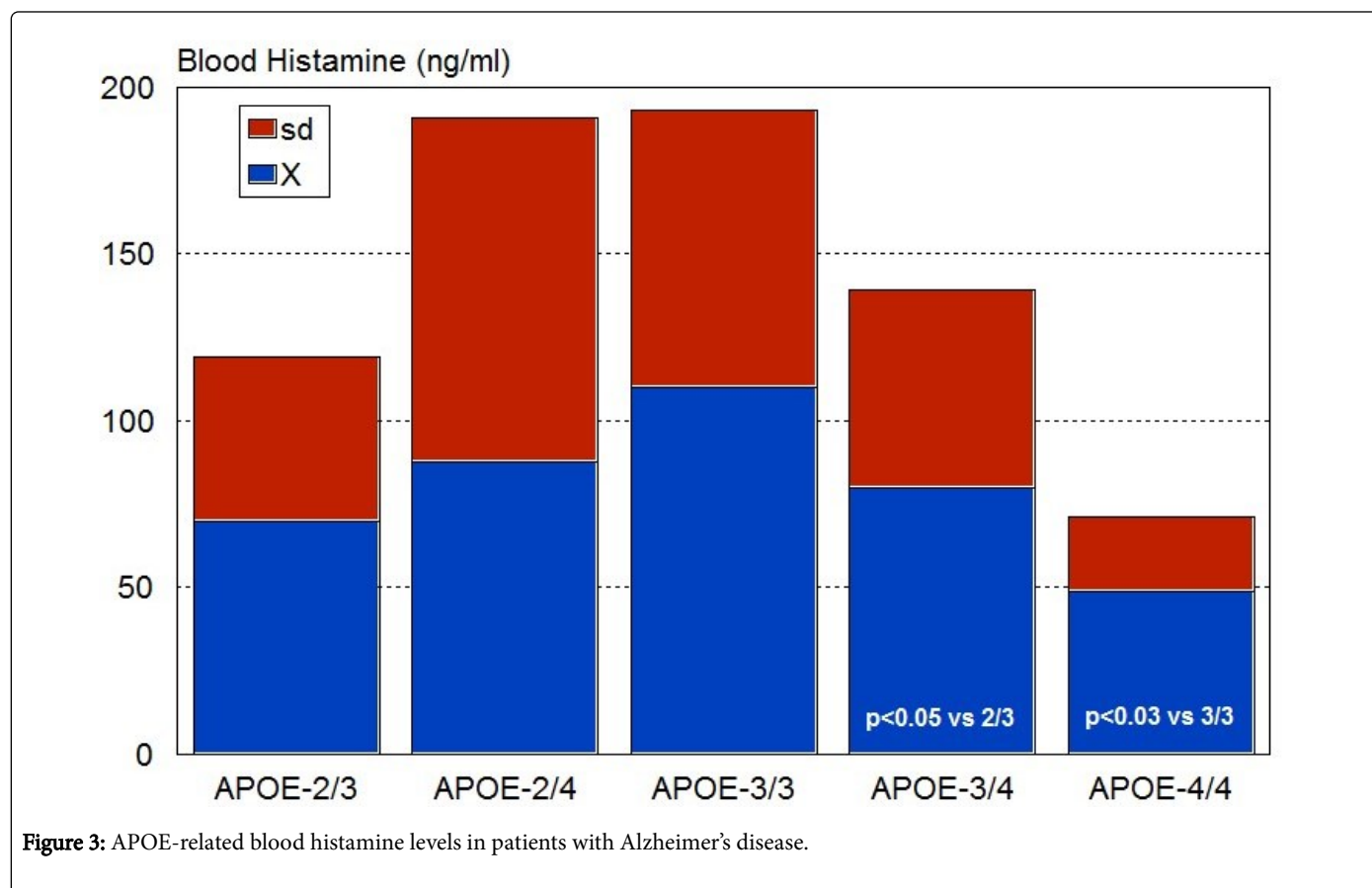


Figure 3: APOE-related blood histamine levels in patients with Alzheimer's disease.

In this context, neuroimmune activation in CNS pathology might be a two-sided reactive phenomenon: (i) neuroprotective, when the stimulus activating the neuroimmune cascade is able to neutralize tissue damage and/or brain dysfunction; and (ii) neurotoxic, when the reactive neuroinflammatory event is persistent and becomes an auto-aggression which magnifies the damage. This Sword of Damocles (dual role) hanging over the CNS and other peripheral tissues under central control must be exquisitely balanced to avoid dangerous decompensation (dominance of neurotoxic effects over neuroprotective effects). This homeostatic equilibrium can be maintained by the interplay of different cytokines, chemokines, neurotransmitters, neuropeptides, neurohormones, and pleiotropic

substances such as histamine. This biogenic amine, acting on different receptors or emanating from different sources (neuronal histamine vs. non-neuronal histamine) can exert dual effects (neurotrophic vs. neurotoxic) on neuronal targets inducing either protection or damage. Therefore, a revival of scientific interest for brain HA would probably be highly beneficial for the good health of neuroscience and neuroimmunology, and also for the better understanding of the pathogenesis of several CNS disorders.

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