

Histamine, antihistamines, and the central nervous system

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ABSTRACT

Histamine is a central nervous system (CNS) neurotransmitter. It acts in the brain via three receptors, H_1 , H_2 , and H_3 . It is a mediator of "wakefulness" and its activity is necessary to maintain wakefulness, alertness, and reaction time. These activities can be impaired by H_1 -antagonists (reverse agonists) capable of penetrating the blood-brain barrier. By blocking the homeostatic effects of histamine in the CNS, drowsiness and functional impairment with or without drowsiness can occur. Several tests have been designed to assess the effects of antihistamines on the CNS. These include subjective measurements of drowsiness and more objective measurements of impairment. Second-generation antihistamines have been designed to minimize blood-brain barrier penetration by reducing lipophilicity and increasing the affinity for P-aminoglycoprotein.

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The first demonstration of histamine in the brain appeared in 1941.¹ Eighteen years later, the observation that it was formed and catabolized in the brain was made.² The discovery that antihistamines caused sedation led to the hypothesis that histamine was a "waking substance."³ Through advances in biochemical methodology and the discovery of histidine-decarboxylase it was learned that histamine exhibited a rapid release and turnover in the brain on a regular basis.⁴ With the discovery of other biogenic means (*e.g.*, catechols and serotonin), research shifted from histamine to these chemicals, which were of profound interest to neuropsychiatry, and attention to histamine as a neurotransmitter temporarily diminished.

More recently, with the discovery and cloning of specific histamine receptors and the observation that the tuberomammillary nucleus in the posterior hypothalamus contains histaminergic neurons that project throughout the central nervous system (CNS), research in the histaminergic system of the CNS has been revitalized.

THE HISTAMINERGIC SYSTEM

The mammillary tubercles of the posterior hypothalamus is the only location in the CNS that contains histidine-decarboxylase and, therefore, the only location capable of synthesizing histamine. Histamine produced here is delivered throughout the brain where it interacts with three of the four known separate histamine receptors (H_1 , H_2 , and H_3). In this manner, it regulates numerous activities responsible for a number of functions (Table 1).

In addition, histamine has intimate relations with other neurogenic transmitters of the CNS. For example, through H_3 -receptors, histamine diminishes cholinergic activity and excites serotonergic neurons. When one traces the connections between the tuberomammillary nuclei and other areas of the brain, it is obvious that histamine is an important CNS mediator exerting its effects through activity at specific anatomic sites throughout the brain (Table 2).

As can be seen, histamine can be considered a homeostatic mediator of CNS functions. The center of control is in the tuberomammillary nucleus. Communication occurs from the nucleus to the other areas where functional activity is expressed *via* the wide distribution of histamine receptors.⁵

HISTAMINE RECEPTORS

So far, four histamine receptors have been cloned. Three of these, H_1 , H_2 , and H_3 , are expressed abundantly in the CNS. All of the histamine receptors belong to the G protein-coupled receptor family. Each

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Table 1 Central nervous system functions of histamine

Attention
Learning
Memory
Wake/sleep cycle
Appetite regulation
Excitation

Table 2 Anatomical sites in the central nervous system affected by histamine

Site	Effect
Dorsal nucleus	Excites serotonergic neurons (diminished serotonin production can result in depression)
Basolateral amygdala	Affects emotional memory
Paraventricular nucleus	Can affect appetite <i>via</i> norepinephrine modulation and controls oxytocin secretion
Magnocellular basal nucleus	Affects cognition <i>via</i> modulation of acetylcholine secretion
Orexin	Affects alertness
Locus caeruleus	Can affect alertness <i>via</i> modulation of norepinephrine secretion

consists of seven transmembrane spanning elements. The general characteristics of each receptor are seen in Table 3.

For the purpose of this review, the H_1 -receptor is by far the most important since H_1 -antihistamines are used to treat allergic disease by acting as reverse agonists of the H_1 -receptor, stabilizing it in its inactive state. When antihistamines enter the brain, the result is a loss of the homeostatic "waking effects" of histamine, potentially reducing alertness, impairing neurological function, slowing reflex time, and resulting in subjective sensations of drowsiness and fatigue. In H_1 -receptor knockout mice there are, because of the loss of activity of histamine, distinct behavioral state abnormalities, thus confirming the role of histamine as an important homeostatic CNS transmitter acting through its H_1 -receptor.^{6,7}

ANTIHISTAMINES

As noted previously, the sedative effects of antihistamines were evident shortly after their discovery. These effects limited the utility of antihistamines in the

practice of medicine, especially in regard to the treatment of allergic rhinitis. Thus, efforts relatively quickly began to develop antihistamines, which were equally efficacious but did not pass the blood-brain barrier and therefore did not produce the side effects noted previously that occur with the abrogation of histamine activity in the brain.

Soon, a group of antihistamines were developed that did not pass the blood-brain barrier or did so only minimally. This group of molecules was designated as "second-generation" drugs. First-generation antihistamines do cross the blood-brain barrier and bind to centrally located H_1 -receptors, whereas those termed second generation either fail to do so or have a markedly diminished capacity to do so.

The factors that effect the ability to penetrate the blood-brain barrier and that have been favorably modified in second-generation drugs are as follows:

1. The lipid solubility of the agent.
2. The affinity of the agent for P-aminoglycoprotein (PGP).
3. Molecular size of the drug.

First-generation antihistamines are usually highly soluble in lipids. This allows for easy passage into the CNS. Second-generation antihistamines are as a rule far less lipid soluble. First-generation antihistamines have little affinity for PGP, whereas second-generation antihistamines usually have a stronger affinity for this transport system. PGP effectively transports drugs from the CNS, and drugs with a high affinity for PGP therefore have less access to the brain.

As a rule, first-generation antihistamines are smaller in size than second-generation antihistamines. It was long thought that this small size also made for easier penetration into the brain. However, the effect of molecular size may be less important than originally posed.

METHODS TO TEST FOR THE EFFECT OF ANTIHISTAMINES ON THE CNS

A drug's ability to penetrate the CNS can be judged in three ways:

1. Subjective assessment of drowsiness.
2. Objective measurements of psychomotor function.
3. CNS receptor binding as assessed by positron emission tomography (PET).

Commonly used assessments for the subjective measurement of sedation and the objective measurement of impairment are seen in Table 4. It should be noted that objective measurements often reveal CNS impairment in the absence of a subjective sense of drowsiness or fatigue. Also, there may be discrepancies between the results obtained by different tests.

Table 3 General characteristics of histamine receptors

Receptor	H ₁	H ₂	H ₃	H ₄
Signal conduction through Location of conductors	G _{q/11} and others Multiple sites throughout the body including smooth muscle bronchi and gastrointestinal tract, cardiac tissue, blood vessels, sensory nerves, endothelium, and CNS	G _s Widely expressed including mucosa of stomach, cardiac tissue, uterus, smooth muscle vascular bed, epithelium of mucosa of nose, submucosal glands in nose, CNS, and immune cells	G _{i/o} Mainly expressed on presynaptic nerves in the peripheral sympathetic adrenergic system and histaminergic nerves in the CNS; receptors can be found in airways and gastrointestinal tract	G _{i/o} and G _{15/16} Eosinophils, neutrophils, basophils, mast cells, spleen, liver, lung, colon, epicanthus, and bone marrow
Chromosome location	3p25, 3p14–21	5q35.3	20q13.33	18q11.2
Signal conduction induces	Increased cyclic GMP, increased intracellular cytosolic calcium, activation of phospholipase C, activation of guanylate cyclase, and nitric oxide production	Increase in cyclic AMP and activation adenylyl cyclase	Decreased cyclic AMP and induction MAP kinase	Decreased cyclic AMP, MAP kinase induction, phospholipase C activation, formation of diacylglycerol, and calcium mobilization
Antagonists (reverse agonists)	Over 40 exist; examples of "second generation" include cetirizine, desloratadine, fexofenadine, loratadine, azelastine, and olopatadine	Burimamide, cimetidine, dimaprit, famotidine, nizatidine, ranitidine, and others (it should be noted that a number of different H ₁ antagonists also show affinity for the H ₂ receptor	None available clinically: Thioperamide, alobenpropit, and others; very little data regarding effect of H ₁ -antagonists on the H ₃ -receptor are available	None available clinically: Has homology with H ₃ -receptor and is also antagonized by same drugs
Activities	Examples of "first-generation" antihistamines are chlorpheniramine, diphenhydramine, pyribenzamine, and others Increases vascular permeability producing a fall in blood pressure, flush, headache, and reflex tachycardia; itch; smooth muscle contraction in bronchi and gastrointestinal tract; stimulation vagal nerve receptors producing reflex smooth muscle contraction in airways; cough <i>via</i> stimulation of sensory nerves in airways; eosinophil chemotaxis; decreased AV node conduction time; enhancement of release of histamine and arachidonic acid derivatives; nitric oxide formation Sneezing, itching, rhinorrhea, and perhaps some degree of nasal congestion <i>via</i> increased vascular permeability with leakage of fluid into the tissues and vasodilatation?	Increased gastric acid secretion; increases vascular permeability producing a fall in blood pressure, flush, headache, and reflex tachycardia; stimulate mucus production in the lungs; direct chronotropic effect on atrium and inotropic action on ventricle; relaxation of esophageal sphincter; stimulation suppressor T cells; decrease neutrophil and basophil chemotaxis and activation; proliferation of lymphocytes; activity of natural killer cells Antagonism of the H ₂ -receptor could potentially reduce the effect of histamine on nasal airway swelling, producing nasal decongestion	Opposes bronchoconstriction and gastric acid; suppression of norepinephrine release at presynaptic nerve endings	Chemotaxis and chemokinesis of mast cells and eosinophils; enhancement of the activity of other chemoattractants (<i>e.g.</i> , chemokines) on eosinophils; up-regulation of adhesion molecules
Nasal symptoms produced			Can produce nasal decongestion by blocking effect of histamine on adrenergic presynaptic receptors	Because histamine can up-regulate inflammation on cells such as eosinophils, H ₂ -antagonists may have a beneficial role in this regard

AMP = adenosine monophosphate; CNS = central nervous system; GMP = guanosine monophosphate; MAP = mitogen-activated protein.

Table 4 Commonly used assessments of subjective drowsiness and objectively measured impairment

Assessment of drowsiness
Epworth sleepiness scale
Karolinska sleepiness scale
Stanford sleepiness scale
Sleep-wake activity inventory
Visual analog rating scale
Objective measurement of CNS impairment
Psychomotor testing such as simulated car driving
Sensory motor coordination speed (reaction time)
CNS arousal (<i>e.g.</i> , flicker-fusion test)
Memory testing
Polysomnography
Multiple sleep latency test
Maintenance of wakefulness test
Oxford sleep resistance test
Aeromedical vigilance test
P300 latency test

CNS = central nervous system.

As one can see, tests to assess the effect of antihistamines on the subjective sensation of drowsiness, more objective performance of CNS functions, and binding to the CNS, look at different aspects of the effect of antihistamines on the function of the brain. Therefore, it would be advisable to look at some of these tests a little closer.

The assessment of drowsiness, such as *via* the Stanford Sleepiness Scale, uses a series of questions. Subjects are usually asked to rate their level of alertness at different times of the day. They are asked questions such as, "Are you feeling active, vital, alert, or wide awake?" They then use a scale rating system to express their subjective sensations.

Tests of CNS function impairment produced by antihistamines might be considered more objective. For example, in the "flicker-fusion test," subjects are required to discriminate flicker from fusion, and *vice versa*, in a set of light emitting diodes; measuring the point or frequency at which the perception of all flicker of an intermittent light stimulus disappears.

In a multiple sleep latency test, an electroencephalogram is used to make a series of recordings monitoring sleep patterns. Eye movements, brain electrical activity, and muscle tone changes are recorded during 15- to 20-minute naps that are spaced about 2 hours apart. These can be used, *e.g.*, to evaluate daytime sleepiness.

The Oxford Sleep Resistance Test is a simple test to assess daytime sleepiness. In this test, a small light-emitting diode is lit for 1 second in every 3, and the subject is asked to respond each time. No electroencephalogram interpretation is necessary.

PET studies differ from the other tests mentioned in that they do not measure either subjective sensation or functional activity, but rather look at the binding activity, in the CNS, of antihistamines. They therefore evaluate H₁-receptor binding. Most PET studies use doxepin C-11 *i.v.* The antihistamine to be studied is given followed by the *i.v.* administration of doxepin C-11 once peak plasma concentrations of the test drug have been achieved. Labeled doxepin will bind to receptors that remain free after the test drug. Thus, the greater the doxepin binding, the less receptors bound by the drug being evaluated. In most instances there is a reasonably good correlation between objective measurements of function and assessment of histamine receptor binding, but there are exceptions to this, and at times the binding activity may not correlate as well as expected with functional assessments.

CLINICAL IMPORTANCE

Obviously, as noted, it is desirable to separate the CNS effects of an antihistamine from its target organ effects, thus eliminating CNS malfunction and/or a sense of fatigue and drowsiness. It is important to know the ability of the drugs we use to pass the blood-brain barrier and thus block the effect of histamine in the CNS. A number of studies have compared the relative activity of these drugs in this regard.

As noted, first-generation antihistamines such as diphenhydramine, chlorpheniramine, hydroxyzine, and promethazine can cross the blood-brain barrier and therefore produce CNS adverse effects. Studies have indicated that each one of these drugs can occupy over 70% of the H₁-receptors in the cortex, hippocampus, pons, and temporal cortex.⁸

Second-generation antihistamines (cetirizine, loratadine, desloratadine, levocetirizine, and fexofenadine), as a rule, have a lesser tendency to penetrate the blood-brain barrier because of a reduced lipid solubility and enhanced affinity for PGP. Thus, they have significantly less effect on CNS function than do first-generation drugs. Cetirizine, at manufacturer suggested dosing, can produce drowsiness. Loratadine and desloratadine can do so at higher than manufacturer suggested dosing. Fexofenadine, however, in doses two to three times the manufacturer suggested dose fails to produce sedation or impairment of psychomotor function.⁸

CONCLUSION

Histamine is a vital neuromediator of the CNS responsible for wakefulness, alertness, and adequate functioning. H₁-antagonists (reverse agonists) that pass the blood-brain barrier can impair such function by binding to H₁-receptors in the CNS. This binding can be reduced or eliminated by reducing lipophilicity and

enhancing interaction with PGP. Tests have been developed to assess both subjective drowsiness and objective impairment produced by antihistamines as well as their binding affinity for CNS H₁-receptors.

All first-generation antihistamines pass the blood-brain barrier, whereas second-generation antihistamines do so less readily or not at all. Cetirizine can do so in suggested therapeutic doses, loratadine and desloratadine in doses above the suggested dose, and fexofenadine does not appear to do so even in doses two to three times higher than the suggested dose.

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