Effect of H_1 antihistamines upon the central nervous system

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The antihistamines have been divided into first and second generation drugs, according to their pharmacokinetic properties, structural characteristics and adverse effects. The effects exerted by these substances upon the central nervous system (CNS) are fundamentally determined by their capacity to cross the blood-brain barrier (BBB) and bind to the central H_1 receptors (RH1). The capacity to cross the BBB is dependent upon the lipophilicity of the drug molecule and on its affinity for P glycoprotein (GpP) – the active transporter of the BBB – which "actively extracts xenobiotic substances from the CNS". GpP is located on the luminal surface of the endothelial cells of the brain blood vessels [1]. The cerebral capillaries present tightly sealing intercellular junctions with a relative lack of transendothelial conduits for the passive diffusion of soluble molecules.

The first generation antihistamines are liposoluble, with scant affinity for GpP – unlike the second generation molecules which are lipophobic and are regarded as GpP substrates. The distinction based on differences in molecular weight (the smaller the molecule, the easier it is to cross the BBB, at least in theory) is becoming increasingly less important. As an example, desloratadine has a molecular weight (mw = 338.9) similar to that of hydrazine (347.9), but permanence of the two drugs in brain tissue differs after administration.

The criterion used to classify an antihistamine as possessing sedative action is based on three requirements that must be met to a minimally acceptable degree:

a) Subjective impact upon sleepiness (presence of drowsiness).

b) Objective evaluations of possible alterations in cognitive and psychomotor function.

c) Central H_1 receptor occupation studies based on positron emission tomography (PET).

Although the last two of these criteria are particularly important, all three must be present to classify the drug as possessing sedative action [2]. Chen et al [3] have studied the different concentrations reached by first and second generation antihistamines in plasma and in brain tissue of normal mice and mice with mdr 1a /1b (multidrug resistance gene encoding for GpP) deficiency. Expressed graphically, the results showed the area under the curve (AUC), reflecting drug penetration of brain tissue, to be much greater (about 5.5-fold) in the case of the first generation histamines versus the second generation molecules.

The histaminergic system

In the CNS, the only neurons to synthesize histamine are found in the mammillary tubercles of the posterior hypothalamus (the only location where histidine decarboxylase activity has been detected), from which projection occurs towards the rest of the brain. Histamine has become just another neurotransmitter. The morphological characteristics of the histaminergic system are similar to those of other biogenic amine systems (norepinephrine, serotonin), i.e., it possesses a compact neuronal nucleus from which many fibers emerge in all directions.

Histamine interacts within the CNS with specific H1-H2-H3 receptors to induce different activities. Histamine in the brain is implicated in many functions, such as the waking-sleep cycle, attention, memory and learning, excitation, and the regulation of appetite. It acts as a regulatory center for global brain activity.

The histaminergic system interacts with other systems and with other neuropeptides to exert the following actions [4]:

a) Modulation of acetylcholine (ACh) release, acting upon the magnocellular basal nucleus, which supplies the cortex with most of its cholinergic innervation. Local histamine application reduces cholinergic tone via the H3 receptors, causing learning difficulties and cognitive impairment.

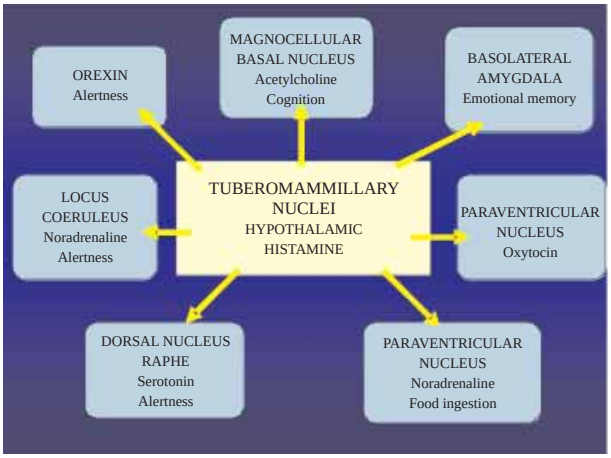

Figure 1. Interactions of the histaminergic system with other neurotransmitter systems of the brain.

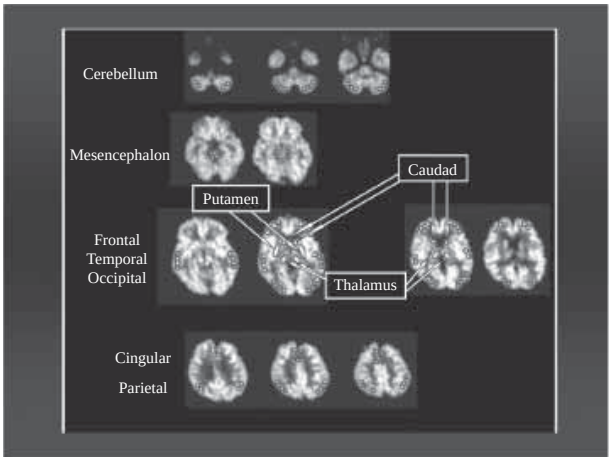

Figure 2. Distribution map of the H_1 histaminergic receptors in the CNS, established by PET-Dox C-11. Reproduced with permission from [10].

b) Modulation of emotional memory acquisition, acting upon the basolateral amygdala.

c) Modulation of alertness; the histaminergic neurons are activated at low level during sleep, and at high level during attention and the waking state. Interaction with orexin-secreting neurons (this being a peptidergic neurotransmitter affecting alertness – its deficiency causing narcolepsy). Interaction, in turn, with the principal noradrenergic nucleus of the brain (the locus coeruleus). Histamine administration in this nucleus increases neuronal excitation in the latter [5].

Lastly, the histaminergic system interacts with and excites the serotoninergic neurons of the nucleus raphe dorsalis [6]. A reduction in serotonin is known to produce depression.

d) Regulation of food intake: histamine is one of the appetite-suppressing neurotransmitters. Noradrenaline, present in the paraventricular nucleus of the hypothalamus, stimulates food ingestion. Histamine has been shown to inhibit noradrenaline release from the nerve endings of the paraventricular nucleus, thereby suppressing appetite [7].

e) Control of oxytocin secretion under different physiological conditions, including delivery and lactation. Histamine acts upon the paraventricular nucleus of the hypothalamus, increasing intranuclear and systemic oxytocin release [8].

To summarize, it can be affirmed that the interactions of the histaminergic system are very numerous and complex, and that the system exerts its different effects by activating different receptor subtypes in different brain regions (Figure 1).

The varied and multiple activities of the histaminergic system are accompanied by a wide distribution of the H_1 receptors throughout the central nervous system.

Studies made with radioactively labeled doxepin (Dox C-11), which acts as a ligand to locate the RH_1 and quantify their occupation, reveal an extensive fixation map within the brain, as evidenced by PET (Figure 2).

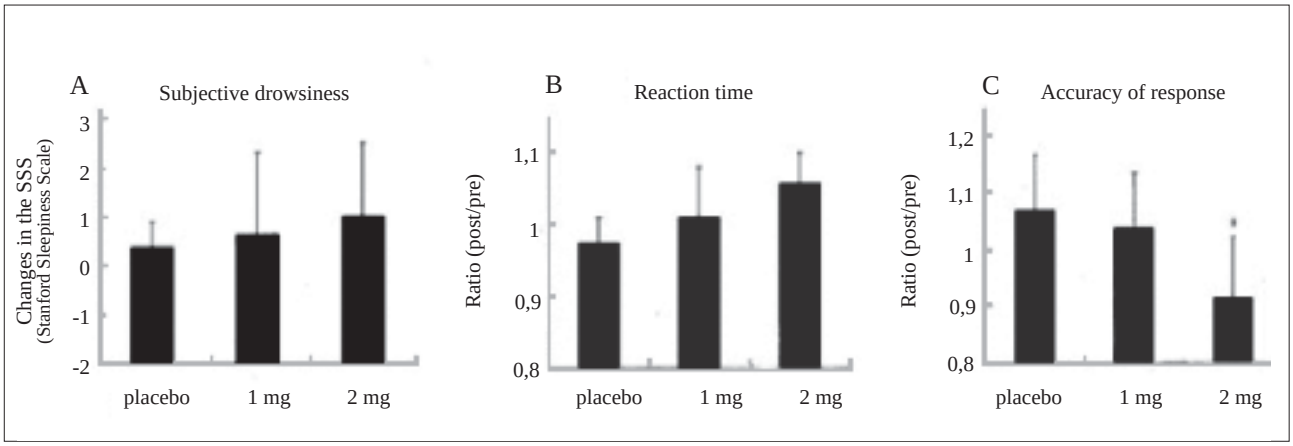

Figure 3. Study conducted with placebo and dexchlorpheniramine (1 and 2 mg). A) Absence of any significant increase in the subjective sleep scale (SSS) with dexchlorpheniramine 2 mg; B) Significant increase in the objective time-response measures (2 mg); C) Reduced accuracy of response (2 mg). Reproduced with permission from [12].

RH_1 occupation studies

Most studies of the central effects of antihistamines, when administered at therapeutic doses, are of a comparative nature between second and first generation molecules, and refer to the alterations caused by the latter group of drugs in reaction capacity, attention, learning capacity or sedation.

As our knowledge of the central effects of antihistamines has increased, objective measurements of such effects gradually have been introduced, since subjective measurements (drowsiness, tiredness) do not correlate adequately to the objective results of functional tests (quantification of reaction time, or of accuracy of response) (Figure 3).

Almost all studies have been based on PET following the administration of Dox C-11 via the intravenous route, and adopting a previously accepted methodology.

PET has become the technique of choice for studying antihistamine penetration of brain tissue. This technique allows the correlation of central H_1 receptor occupation to psychometric and functional studies.

To determine the amount of H_1 receptors occupied by each drug, the study antihistamine is administered, followed by intravenous Dox C-11 injection once the peak plasma drug concentration has been reached. The RH_1 are expressed as the zones of Cox C-11 "binding potential" (BP), i.e., Dox C-11 binds to the receptors that remain free after the study antihistamine has been administered. If the antihistamine in question shows little or no binding to the RH_1, then the BP sites will be very numerous. Such an antihistamine can thus be taken to represent a drug with little or no central effects (second generation molecule). If binding to the receptors is extensive, then practically no sites will remain for Dox-11 binding, as in the case of the first generation antihistamines.

Tagawa et al [9] (Figure 4), in a placebo controlled study involving ebastine 10 mg and chlorpheniramine 2 mg, showed most of the radioactivity to be located frontal, temporal and occipital cortical regions of the brain, the cingulate gyrus, the striate nucleus and the thalamus. Nevertheless, despite the fact that these regions are very rich in RH_1, another study indicates that Dox C-11 binds nonspecifically within the striate nucleus and thalamus, in a proportion that exceeds the extent to be expected on the basis of the number of H_1 receptors present in these areas. Postmortem studies have shown that the density of these receptors in the subcortical zones is slightly lower than in the cortical regions; consequently, the high Dox C-11 distribution values in these locations would not precisely reflect the actual RH_1 density [10].

Cerebellar uptake is generally low, since few RH_1 are found at this level. The cerebellum is usually taken to be an area of nonspecific Dox C-11 fixation - the result at cerebellar level being subtracted from the findings of other regions in order to obtain more precise quantification in the latter.

Comparison by graphic analysis of these images after administering the antihistamines revealed the areas where chlorpheniramine fixation is greater, i.e., the zones where the latter occupied more H_1 receptors than ebastine. These zones were fundamentally the prefrontal and frontal cortex, the cingulate gyrus and the thalamus.

The occupation of brain RH_1 was correlated to the plasma levels of chlorpheniramine, and in turn to a worsening of cognitive function. However, this was not observed in the case of ebastine (specifically its active metabolite, carebastine). In effect, ebastine occupation was approximately 10%, while chlorpheniramine 2 mg exceeded 50%. The RH_1 occupation percentages for the rest of the second generation antihistamines range from 10-30% (cetirizine), though fexofenadine has been reported to occupy no RH_1 [11].

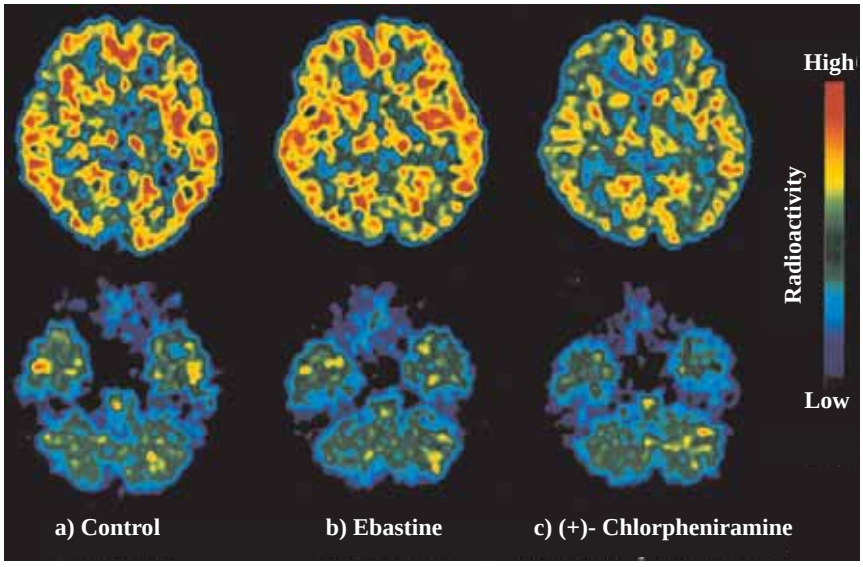

Figure 4. PET Dox C-11 measurement of central RH_1 occupation by first (dexchlorpheniramine) and second generation antihistamines (ebastine). The BP (receptor binding potential for Dox-C11) is greater with ebastine (fewer occupied H_1 receptors, with increased Dox C-11 binding; increased radioactivity) than with dexchlorpheniramine (more occupied H_1 receptors, with decreased Dox C-11 binding; lesser radioactivity). Reproduced with permission from [9].

In order to define an antihistamine as being non-sedative, its occupation of the central receptors should not exceed 20%, when administered at the recommended maximum dose [2].

Central manifestations appear after the occupation of over 50% of the brain RH_1 [9], though some authors are of the opinion that such occupation must reach 60% or even 70% [12].

Another approach to the study of neuronal activity is to measure global (CBF) and regional cerebral blood flow (r-CBF). The cerebral circulation has its own self-regulating system that maintains brain perfusion constant between mean arterial pressure values of 60-160 mmHg. Myogenic and metabolic mechanisms account for this phenomenon. From the metabolic perspective, the metabolic demands determine arteriolar tone. If the demand exceeds the existing blood flow, then metabolites are released that induce vasodilatation. These include hydrogen ions, nitric oxide, adenosine and prostaglandins [13]. Okamura et al [12], in the course of visual discrimination tests, found no differences in CBF between chlorpheniramine and placebo, though differences in r-CBF were noted – with increments in the anterior cingulate circumvolution and prefrontal cortex of the right side.

Both brain regions form a very important part of the extensive neuronal network in charge of spatiotemporal attention [14] – the speed of response in activities where these regions are implicated depending on the cingular zone (composed of long association fibers among different areas) [15].

This represents an increase in blood perfusion demand for the conduction of visual discrimination and motor selection cognitive processes, i.e., it is more difficult to maintain attention or alertness under such circumstances (under the effect of d-chlorpheniramine), and these brain regions require more perfusion to continue their function.

On the other hand, a decrease in subcortical activity was recorded. PET has been used to show that the subcortical reticular formation and the thalamic intralaminar nuclei are activated when the subject is instructed to change from a state of relaxation to a state of important alertness and attention. The described decrease in activity at this level would reflect transition from alertness to relaxation following administration of the antihistamine.

Cetirizine is possibly the second generation antihistamine most commonly used in studies of this kind, though investigations and comparisons have been made with all those molecules commonly used in adults.

Special situations

Pediatric patients

In children, most of the studies made with second generation antihistamines, including the ETAC involving 817 children treated with cetirizine for 18 months, have observed no adverse effects of interest in relation to cognitive or psychomotor function [16-18].

Only Ng et al have demonstrated an increase in latency, using the P300 ERP (a test evaluating time to response after an auditory stimulus), after the administration of a single dose of cetirizine 10 mg, though the children showed no subjective drowsiness [19].

Interaction with alcohol

The first generation antihistamines reinforce the effects of ethanol upon oculomotor coordination, cognitive function and driving.

In most cases no such effects have been observed with the second generation antihistamines [20,21], though no categorical affirmations can be made in this sense. In the case of combining alcohol with antihistamines, Weiler et al have found first generation drugs to manifest more central effects than the second generation antihistamines – though the latter also impair activities. It has even been affirmed that the first generation drugs induce more deleterious effects upon vehicle driving than alcohol, at the doses studied [2].

Conclusions

In general terms, and after establishing different visual and oculomotor tests requiring attention, signal detection and identification (acoustic, visual), and decision taking to assess alterations in brain function, the second generation antihistamines administered as a single dose or in the course of 4-5 days did not differ significantly from placebo as regards the results obtained [23-28]. In contrast, the first generation molecules showed alterations in the tests performed.

Nevertheless, tolerance is known to develop, with a marked decrease in central effects of the first generation antihistamines when the latter are administered for 4-5 consecutive days [29,30].

Nevertheless, it must be taken into account that the great majority of the studies to date have been made in healthy volunteers. This makes it difficult to fully extrapolate the results to the rest of the population, since allergic patients are influenced by inflammatory mediators present in the physiopathology of the allergic inflammation process - and this may induce variations in capillary permeability, not only at peripheral level but also at the blood-brain barrier. These variations in turn may lead to differences in the central adverse effects of such drugs in these patients.

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