Introduction

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Since the discovery of histamine in 1910 there has been growing evidence that this biogenic amine, which is mainly synthesized by mast cells and basophils, is released in inflammatory processes, and plays a fundamental role in the pathogenesis of allergic rhinitis.

Histamine is a biogenic amine found in many body tissues and cells. It is synthesized from the amino acid L-histidine through mediation of the enzyme L-histidine decarboxylase, while its metabolism is mediated by the enzyme histamine N-methyltransferase, or alternatively by diamino-oxidase. Histamine is an important chemical messenger with stimulatory action (agonism) upon at least four types of receptors, and with multiple regulatory functions in the nervous system, gastrointestinal tract and immune system. All histamine receptors transmit the corresponding extracellular signals via protein G systems coupled to intracellular second messengers. The activation of one of these messengers, specifically guanosine triphosphate (GTP) – binding protein, triggers a cascade of events at intracytoplasmic level that ultimately induce activation of the kappa nuclear factor (NF-κ). The latter is an important proinflammatory transcription factor that exerts its function by binding to the promoter regions of genes – thereby stimulating the synthesis of a large number of mediators [1].

Until recently, it was believed that the H_1 antihistamines were blockers (antagonists) of the H_1 receptors. However, recently it has been shown that the H_1 receptors may present two different conformational states: active and inactive [2]. Histamine acts as an agonist by binding to and stabilizing the active conformation of the receptor, thereby deviating the balance in favor of an activation state. In the same way, the H_1 antihistamines combine with and stabilize the inactive form of the receptor (inverse agonism), thereby deviating the balance in favor of the inactive receptor conformation. According to this model, the receptor is chronically "turned on" even in the absence of an agonist, and the degree of activation under conditions of equilibrium constitute its baseline activity level.

Possibly some antihistamines that may be developed in future will behave as neutral antagonists, i.e., they may combine with both H_1 receptor conformations without affecting baseline activity, but preventing the binding of an agonist (neutral agonism).

The relative number of receptors occupied by histamine or by a given antihistamine depends on the relative concentrations of these substances in the proximity of the receptor. In immediate hypersensitivity reactions, histamine reaches concentrations of 10^{-5} to 10^{-3} M in the implicated tissues – this being 1000 times greater than the concentration of leukotrienes and other potent chemical mediators of inflammation. It is important to point out that while the tissue concentration of an antihistamine varies according to the dose administered and its pharmacokinetic characteristics, levels of 5×10^{-6} M are rarely reached. Nevertheless, many antihistamines have active metabolites, and the concentration of the latter may be higher and with greater clinical relevance than the original compound [3].

The term pharmacokinetics refers to the passage of a drug substance through the body, i.e., its absorption, distribution, metabolization and elimination. On the other hand, when speaking of pharmacodynamics, we refer to properties of the drug such as its mechanism of action, potency, effects and toxicity.

The great majority of second-generation antihistamines have shown added antiinflammatory properties, most of which have been observed *in vitro* and in experimental models in animals and humans – though not secondary to natural exposure. It has been suggested that these antiinflammatory properties could be established in sustained chronic treatments with such drugs [2].

In the last 20 years, pharmacological research has developed compounds with increased potency, longer lasting action, faster action, and improved safety profiles. A recent publication considered that the ideal pharmacological properties of an antihistamine could be summarized as follows: potent and selective H_1 receptor blocking action, added antiallergic activity, no interference on the part of food or other concomitant medication, and no interaction with the P4503A cytochrome [4].

Antihistamines constitute very effective treatment in patients with intermittent and persistent allergic rhinitis [5]. It has been shown that pharmacological inhibition of histamine action markedly reduces the nasal symptoms of patients with this illness. The antihistamines are among the most widely used drugs in the world. In primary care alone, 90% of all cases of allergic rhinitis are treated with these drugs [6].

The present monograph addresses the most relevant pharmacological aspects relating to the pharmacokinetics, pharmacodynamics, interactions, and comparative

pharmacology of the different antihistamines, their side effects upon the cardiovascular system, central nervous system, and impact upon psychomotor performance and patient ability to drive.

References

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