基礎篇：組織胺與組織胺受體

The Basics: Histamine and Histamine Receptors

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Histamine is a biogenic amine with profound effects in various physiological and pathological conditions. Histamine is synthesized in many different types of cells by the decarboxylation of histidine, which is mediated by vitamin 6-containing histidine decarboxylase. Histamine is stored in vesicles or granules of mast cells, basophils, neuron & enterochromaffin-like cells of GI tract and released upon stimulation. Nevertheless, it is synthesized and immediately released in other cell types. Apart from the endogenous source, histamine is present in exogenous sources, including several types of food and synthesis during microbial fermentation or by microbiota in the gut. Histamine is metabolized through two pathways. Histamine N-methyltransferase (HNMT) expressed in central nerve system, intestine, liver and kidney is the major enzyme to catalyze histamine inactivation. Diamine oxidase (DAO) in the small intestine, liver, kidney, placenta, skin, and eosinophils, catalyzes the rest of histamine in the body. DAO and HNMT present in intestinal epithelium function as barrier to prevent the passing of histamine in ingested food to blood circulation to provoke histamine-mediated symptoms. Histamine exerts its biological effects through binding to its four receptors (H1R, H2R, H3R, H4R), which belong to G-protein coupled receptor (GPCR) family. These receptors are derived from four different gene products with low homology. The binding affinities of H1R and H2R to histamine are relatively lower than these of H3R and H4R. Histamine receptors conserve constitutive activity in the absence of histamine. At resting state, receptor exists in dynamic equilibrium between inactive and active conformations. Agonist binding shifts the equilibrium to active conformation, and inverse agonist preferentially binds to inactive conformation. The antagonist binds to both active and inactive conformations and has no effect on the equilibrium. Many antihistamine drugs are inverse agonists. H1R-H4R activation elicit distinct signaling pathway via coupling to different Gα subunits of G protein complex. H1R mediates the bronchoconstriction and increased vaso-permeability during allergic reaction. It is also involved in the regulation of food intake and wake-sleep in CNS. H2R is mainly responsible for gastric acid secretion in GI tract and also has a role in the regulation of immune cells. H3R is mainly expressed in CNS to regulate neurotransmitter release, sleep-wake, food intake, attention and recognition. H4R is expressed primarily in hematopoietic cells and modulate cytokine expression and immune response. Given that histamine receptors are expressed in wide ranges of cell types and many immune cells express more than one histamine receptors, the pathological roles of histamine involved in allergic and inflammatory diseases are rather complicated. For instance, in

allergic asthma histamine is not only participating in the immediate type I reaction, it also has roles in the early sensitization and allergic inflammation in the late phase. Anti-histamine drugs targeting H1R are not effective for treatment of asthma, implicating the involvement of other histamine receptors in the disease manifestation. Considering the complexity of histamine involved in many physiological and pathological conditions, it is apparent that the development of receptor-specific antagonists would be crucial for the effective treatment of various diseases associated with histamine.