Histamine Receptors 13/05/2020

Histamine is a bioactive amine that acts as a signalling molecule and neurotransmitter. It exerts its diverse biological effects through the activation of 4 types of membrane bound receptors from the aminergic G-protein coupled receptor family: H_1, H_2, H_3, and H_4.

The H_1 and H_2 receptors (Gq- and Gs-coupled, respectively) are classically considered postsynaptic receptors, whereas the H_1 receptor activates the phospholipase C-phosphokinase C pathway and the H_2 receptor activates the phosphokinase A pathway .

The H_3 receptor is Gi-coupled and localized pre- and postsynaptically, whereas it has predominantly been studied as an autoreceptor. Blocking of the H_3 receptor enhances histamine release that in turn modulates neuronal function and plasticity and has been proposed as a treatment of mental disorders.

The histamine H_4 receptor was only recently discovered; it seems to have mainly immunological functions, and its distribution and function in the CNS are still somewhat debated.

The 4 histamine receptors are heptahelical G-protein coupled receptors (GPCR), encompassing a diverse group of membrane receptors composed of a single polypeptide that is folded into a globular shape, forming a 7-transmembrane structure. The extracellular loops are responsible for signalling molecule binding (N-terminal) . The third and fifth transmembrane domains of H_1 and H_2 receptors contribute to histamine binding

Histamine receptor expression and function

The H_1 receptor is widely distributed throughout the body, with well-documented expression in the central nervous system (CNS), smooth muscle, sensory nerves, heart, adrenal medulla, as well as immune, endothelial, and epithelial cells. It mediates most of the postsynaptic effects of histamine within the CNS. Through binding of the transmembrane domains of H_1 receptor, histamine stimulates smooth muscle contraction in the respiratory and gastrointestinal tract, stimulates sensory nerves leading to pruritus and sneezing, and increases vascular permeability (through prostacyclin, platelet activating factor, von Willebrand factor, and nitric oxide; NO) leading to oedema. H_1 receptor intracellular signals are transmitted through Ca^{2+}, cGMP, phospholipase D, phospholipase A2, and NF-κB activation.

The H_2 receptor is widely expressed and can be found in gastric mucosal cells, heart, CNS, immune cells, and smooth muscles of the airway, vasculature, and uterus. H_2 receptor activation leads to activation of cAMP-dependent and -independent pathways (adenylate cyclase, c-Fos, c-Jun, PKC, p70S6K). Differential levels of cellular expression result in the stimulation of hydrochloric acid secretion from acid secreting parietal cells of the gastric mucosa, smooth muscle relaxation of

the vasculature and airways, increased cardiac rate and contractility, and immunomodulatory effects through basophil suppression .

The H_3 receptor is predominantly expressed in the CNS (basal ganglia, hippocampus and cortical areas), but can also be found in the peripheral nervous system, airways, the cardiovascular system, the gastrointestinal tract and on mast cells. Acting through the presynaptic H_3 receptor, histamine regulates its own release (negative feedback) as well as the release of other neurotransmitters such as noradrenaline, dopamine, serotonin, acetylcholine, and gamma-amino-butyric acid. In the lower airways, H_3 receptors are located on postganglionic cholinergic nerves and counteracts bronchoconstriction, through stimulation of phospholipase A2 . In the upper airways, histamine may play a role in nasal congestion through its activity at H_3 receptors. The intracellular pathways related to H_3 receptor activation are enhanced Ca^{2+} influx, MAP kinase, and inhibition of cAMP.

The H_4 receptor shows the highest level of expression in bone marrow and peripheral blood leukocytes but is also found in spleen, thymus, lung, gastrointestinal tract, liver, peripheral nerves, and central neurones in the cerebellum and hippocampus . H_4 receptor activation induces calcium mobilisation through cAMP in mast cells .