

# The histaminergic system in brain: neurophysiology

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The histaminergic neurons in the tuberomammillary nucleus (TMN) send their axons all over the central nervous system. They are active during waking but not during sleep and represent the major waking centre of the brain. Three of the four known histamine receptors are widely expressed in the brain. Mutual interactions with other aminergic systems (acetylcholine, norepinephrine, dopamine, serotonin) and peptidergic (orexins/hypocretins) systems form a network with basic homeostatic functions that are connected with the sleep-waking regulation. Histaminergic neurons fire regularly at less than 4 Hz at a membrane potential of about -50 mV. They display two typical currents, an A-type inactivating outward current and  $I_h$ , an inwardly rectifying cation-current.  $Ca^{2+}$ -dependent prepotentials in the dendrites and a tetrodotoxin sensitive, non-inactivating  $Na^+$ -current together with a post-spike  $K^+$ -current create a pacemaker cycle. The firing rate is variable during waking dependent on behavioral state. A GABAergic inhibition mainly from the ventrolateral preoptic area (VLPO), a known sleep active nucleus stops the firing during sleep.

## Transmitters acting on histaminergic neurons

*Amino acids:* Glutamatergic fibers from the cortex and the hypothalamus provide an excitatory input, through AMPA- and NMDA-receptors. Glycine inhibits a subpopulation of histaminergic neurons but glycinergic fibers are uncertain. Taurine, an osmolyte that can reach relevant concentrations in the extracellular space, gates strychnine-sensitive glycine receptors and GABA<sub>A</sub>-receptors. GABA<sub>A</sub>-receptors are heterogeneous with different GABA sensitivities, depending on GABA<sub>A</sub>R-subunit expression. The sedative component of general anaesthesia (e.g. propofol) is attributed to an action on the TMN: cessation of firing is associated with the loss of consciousness.

*Amines:* The aminergic nuclei are mutually connected, they are all functionally excitatory on the TMN but use a variety of mechanisms. A nicotinic fast desensitizing action occurs through  $\alpha 7$ -type receptors. Noradrenaline does not affect histaminergic neurons directly but effectively controls GABAergic input through  $\alpha 2$ -receptors. Dopamine also excites histamine neurons through a yet undefined indirect action. Serotonin excites the histaminergic neurons through activation of the electrogenic  $Na^+$ - $Ca^{2+}$ -exchange (NCX).

*Peptides:* Galanin inhibits TMN firing. It is thus possible that galanin participates in both the autogenic (feedback) inhibition and the extrinsic inhibition from VLPO. Orexin/hypocretin containing neurons are neighbours in the TMN, the nuclei intermingle partially. Both hypocretins excite histamine neurons through the Hcr2 receptor and largely activation of  $Na^+$ / $Ca^{2+}$  exchange (NCX). Hypocretin neurons also express dynorphin which suppresses GABAergic input. The appetite stimulating ghrelin inhibits a potassium channel (Kir3) in TMN. Nociceptin strongly inhibits TMN neurons at the postsynaptic level while morphine ( $\mu$ -receptors) excites them through disinhibition.

*Purines:* The TMN expresses adenosine deaminase; adenosine is a sleep-pressure substance but does not affect TMN. In contrast, ATP excites TMN through P<sub>2</sub>Y<sub>1</sub> and P<sub>2</sub>Y<sub>4</sub> receptors.

### Histamine actions in the brain

The projections to thalamus and cortex, as well as to other aminergic nuclei and their emanating axons are responsible for the waking action of histamine. Relay cells in the thalamus are depolarized and thus shifted to the regular firing mode, which represents the open door of perception. In the absence of histaminergic tone, these cells fall into the burst firing mode, which closes the gate to the cortex for sensory input. Most targets are depolarized and excited through a number of different mechanisms. On the other hand histamine can block a  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$ -conductance and thus the accommodation of firing through another receptor ( $\text{H}_2$ ). Some hippocampal interneurons are rather strongly excited by  $\text{H}_2$ -receptor activation making the overall histamine action in this structure an inhibitory one.

Ionotropic receptors: Histamine can activate chloride conductances in thalamus and hypothalamus: in the supraoptic nucleus this effect is blocked by picrotoxin and  $\text{H}_2$ -receptor antagonists. In thalamic interneurons it is also  $\text{H}_2$ -receptor mediated but not picrotoxin sensitive. If any, histaminergic ionotropic receptors seem to play a minor role in the vertebrate brain. In contrast, arthropod sensory neurons, the insect eye photoreceptor and lobster olfactory neurons display synaptic transmission through histamine-gated chloride channels. Four metabotropic histamine receptors have been cloned,  $\text{H}_1$ ,  $\text{H}_2$  and  $\text{H}_3$  occur in the brain.  $\text{H}_4$ -receptors are mainly expressed in peripheral tissues such as blood, spleen, lung and liver.

$\text{H}_1$ -receptor activation causes excitation in most brain regions (brainstem, thalamus, hypothalamus, cortex, amygdala, striatum) through  $\text{G}_{q11}$  protein and a direct block of a leak potassium conductance or phospholipase C, inositoltrisphosphate (IP3) and diacylglycerol (DAG) mediation. IP3 releases  $\text{Ca}^{2+}$  from internal stores and activates a number of  $\text{Ca}^{2+}$ -dependent processes, including the opening of a cation channel (TRPC) or the stimulation of a  $\text{Na}^+$ - $\text{Ca}^{2+}$ -exchanger (NCX). Furthermore, the elevated intracellular  $\text{Ca}^{2+}$  can stimulate NO-synthase and consequently guanylate cyclase. On the other hand  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  channels can be opened leading to hyperpolarisation and inhibition for instance in hippocampal pyramidal neurons.

$\text{H}_2$ -receptors: Activation of  $\text{H}_2$ -receptors blocks a  $\text{Ca}^{2+}$ -activated potassium conductance (small K) which is responsible for the accommodation of firing and a long lasting afterhyperpolarization following action potentials. The accommodation of firing determines the number of action potentials in response to a longer (ca 100 ms) depolarizing stimulus and the amount of  $\text{Ca}^{2+}$  inflow through high voltage activated  $\text{Ca}^{2+}$  channels or NMDA-channels. These actions are mediated by cyclic AMP and PKA, which leads to phosphorylation of the transcription factor CREB. Cyclic AMP can also interact directly with another current, the hyperpolarisation activated cation current (I<sub>h</sub>). Brief exposure of hippocampal slices to histamine or cyclic AMP causes long-term enhancements of CA1 population spikes and pyramidal neurone firing in the absence of high frequency stimulation.

The  $\text{H}_3$ -receptor was found by the group of J-C Schwartz in Paris in 1983.  $\text{H}_3$ -autoreceptors are present on TM neuron somata, dendrites and axons. They are coupled directly through a  $\text{G}_i/o$  protein to  $\text{Ca}^{2+}$  channels causing inhibition of TM neuron firing, of histamine release from varicosities and of histamine synthesis. Adenylyl cyclase is depressed by  $\text{H}_3$ -receptor activation. Importantly  $\text{H}_3$ -receptors are inhibitory on many non-histaminergic varicosities such as those containing glutamate, ACh, dopamine, noradrenaline, serotonin, GABA and various peptides.

Synaptic plasticity: Histamine also causes long lasting changes in synaptic transmission and it modulates other forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) that are associated with learning and memory. An important signal transduction pathway is the transient rise of

intracellular  $\text{Ca}^{2+}$  and its binding to a  $\text{Ca}^{2+}$ -Calmodulin Kinase. Histamine potentiates directly the NMDA receptor (NR2B subunit) especially in slightly acidic conditions. Histamine strongly promotes burst firing in the hippocampus leading to 200Hz oscillations (ripples). The replay of ripples during sleep has been proposed as critical for memory consolidation.

### **Some reviews (containing neurophysiology)**

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