



HISTAMINE RECEPTORS & SLEEP/WAKE CYCLES

by Regina Patrick RPSGT

Histamine is a substance that is present in all body tissues but particularly the gastrointestinal tract, lungs, red blood cells, mast cells, heart, and central nervous system. It has different functions in each of these tissues. For example, it stimulates gastric secretions in the gastrointestinal tract; contracts smooth muscle in the lungs; dilates blood vessels; mediates the activity of mast cells in allergic reactions; increases heart rate, and it has neurotransmitter-like activity in the central nervous system (CNS) where it plays a role in wakefulness and in the alternation between sleep and wake cycles. Its effect on sleep and wake is of interest to scientists as they work to determine how to strategically use histamine to treat sleep disorders that involve disruptions of sleep/wake cycles such as insomnia, hypersomnia, narcolepsy, and circadian rhythm disorders.

Scientific interest in the chemical processes involved in life ultimately led to the discovery of histamine. In the late 19th century the chemical composition of a cell's nucleus was the focus of much scrutiny as scientists sought to understand the chemical processes involved in life. One outgrowth of this scientific interest was the discovery of histidine in 1896 by German physician and researcher Albrecht Kossel. Researchers soon investigated the new amino acid to learn its physiological effects, its chemical structure, and its synthesis and metabolism in the body.

In 1907, Windaus and Vogt, while working to uncover the chemical structure of proteins and amino acids, subjected histidine to the actions of hydrochloric acid (HCl) and sodium nitrite (NaNO₂) which yielded histamine as a by-product. They considered the new substance as a curiosity but other researchers thought that the by-product potentially had scientific value. George Barger and Henry H. Dale in 1910 were the first to investigate physiological effects of histamine. Early studies by these and other researchers showed that histamine was a potent vasodilator; it could trigger a drop in blood pressure; it could contract smooth muscles in certain organs (e.g., the bronchioles, bladder, and gastrointestinal tract); and it could increase secretion of bile, saliva, and pancreatic juices.

By the 1930s, scientists began to suspect that histamine may have neurotransmitter-like activity. In 1931 for example, MacGregor and Peat speculated that the cellular release of histamine may be neurally mediated. This speculation was influenced by previous research that indicated vasodilation resulted from antidromic transmission (i.e., traveling in a direction opposite from normal) of a histamine-like substance. To test their speculation, MacGregor and Peat removed one lung in cats and measured the histamine content of the

lung tissue. Later, they chemically stimulated the pulmonary nerve in the remaining lung in the cats and then removed lung tissue from the animals. On measuring the amount of histamine in the unstimulated and stimulated lung tissues, the researchers did not note any difference. Although they were to conclude from this that neural activity was not involved in histamine release, the possibility still remained of scientific interest.

By the late 1930s and continuing into the 1940s, the first anti-histamine drugs – pyrilamine, diphenhydramine, tripelemamine, chlorpheniramine – were developed. Scientists soon learned that the antihistamine effect on an organ (e.g., decreased gastric secretion) varied among the antihistamine drugs. In 1948, Bjorn Folkow et al. proposed that this finding indicated that more than one histamine receptor may exist. With this in mind, Arunlakshana and Schild in their 1959 study noted that the ability of the antihistamine mepyramine to block histamine's effect (in this case, contraction) on a guinea pig's heart differed from its ability to do so on the animal's ileum. They concluded that two different receptors on the organs explained this response. Schild and coworker A. S. Ash in 1966 were able to validate the existence of the H1 receptor. They subjected guinea pig ileum and other tissues to various antihistamines. The drugs' histamine blocking effect on these tissues matched that of mepyramine. This suggested that all of these tissues contained one subtype of a histamine receptor. The receptor was named the H1 receptor. Black et al. discovered the H2 receptor in 1972; Arrang et al. discovered the H3 receptor in 1983 and Oda et al. discovered the H4 receptor in 2000.

H1 and H3 receptors have been the most extensively studied concerning their roles in sleep and wake. The H2 receptors play a role in sleep and wake but most research has focused on their role in the gastrointestinal tract since H2 antagonists decrease stomach secretions. (As a result, H2 antagonist drugs are primarily used to treat ulcers and gastric reflux.) H4 receptors are primarily being studied for their role in modulating the immune response, especially the allergic response.

Most histaminergic cells in the brain are found in the hypothalamus. Animal studies suggest that the tuberomammillary nucleus (TMN, a group of cells located in the lower portion of the hypothalamus) is the wake center.

Histaminergic neurons arise out of the TMN and insert into the frontal cortex, anterior hypothalamus, thalamus, and brain-

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stem. Scientists are not fully sure but believe these ascending pathways induce wakefulness by either directly stimulating cortical neurons or indirectly by inhibiting the activity of the anterior hypothalamus which plays a role in inducing sleep.

Histaminergic neurons descend from the posterior hypothalamus and insert into the the rear portion of the pons (i.e., the mesopontine tegmentum). In the mesopontine tegmentum, histaminergic neurons lie in close proximity to cholinergic, adrenergic, and gamma-amino butyric acid transmitting (i.e., GABAergic) neurons. (All of these neurotransmitters are stimulatory.) The interplay between histaminergic neurons and the cholinergic, adrenergic, and GABAergic neurons play a role in the onset and duration of REM sleep and the alternation of sleep/wake cycles.

H1 receptor's role in sleep

Histamine in conjunction with the hypothalamic stimulatory neuropeptide orexin may induce and maintain wakefulness through H1 receptors. Zhi-Li Huang et al. in their 2001 study found that H1 receptor knock-out mice (i.e., mice who lack the H1 receptor) are less physically active than normal mice. The animals' activity did not increase when the researchers injected them with orexin suggesting that the H1 receptor plays a role in mediating wakefulness.

H2 receptor's role in sleep

Although the H2 receptors have not been as extensively studied for their role in sleep, they seem to mediate wakefulness in a similar fashion as the H1 receptors. Studies show that H2 agonists increase wakefulness8 and H2 antagonists increase sleepiness and shortens sleep latency onset.

H3 receptor's role in sleep

Animal studies suggest that H3 receptor agonists increase both sleep time and the amount of slow wave sleep. Conversely, H3 receptor antagonists increase wakefulness and decrease the amount of slow wave sleep and decrease the amount of rapid eye movement (REM) sleep. Scientists hope that this last effect – decreased REM sleep – may allow H3 antagonists to block the improper manifestaton of REM sleep features (e.g., muscle atonia resulting in cataplexy) in people with narcolepsy. Results of several H3 antagonist drug studies are promising. In animal studies, the H3 antagonists GT-2331 and JNJ-10181457 decrease the frequency and duration of cataplexy episodes in dogs. Barbier et al. in their 2004 study found that the drug JNJ-5207852 is selective for the H3 receptor; it can cross the blood-brain barrier (they gave the drug subcutaneously to their animal subjects); it increases wakefulness without rebound hypersomnolence; it decreases REM sleep; and it does not cause hypermotility with its stimulatory effects. Currently, the drug GSK189254, a selective H3 receptor antagonist, is undergoing investigation to see if it can be used in treating narcolepsy in humans. Primarily, scientists are interested in learning if the drug can improve wakefulness and, secondarily, if the drug can reduce the frequency and severity of cataplexy and other night-time symptoms (e.g., sleep paralysis) of the disorder.

In the past, the sedating quality of antihistamine drugs was considered an annoying side effect. It has only been in recent years with the advent of the discovery of (at this point) four histamine receptor subtypes that scientists have begun to consider that histamine receptors may have a role in sleep and wake. Research is now shifting to determine how to manipulate the function of the receptors – especially H1 and H3 – in order to improve the sleep (or wakefulness) of people struggling with insomnia, hypersomnia, narcolepsy, and circadian rhythm disorders.

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