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Histamine in the central nervous system: its role in circadian rhythmicity

Jerzy Z. Nowak

Department of Biogenic Amines, Polish Academy of Sciences,
3 Tylna St., 90-950 Łódź, Poland

Abstract. Histamine is an accepted neurotransmitter and/or neuromodulator in the central nervous system (CNS). Its neuronal system in the brain is well organized, with cell bodies localized in a small area of the posterior hypothalamus. Diverse biological actions of histamine are mediated via three classes of receptors termed H_1, H_2, and H_3. The existence of other histamine receptor subtypes is likely in invertebrates or in birds. This article surveys basic data indicative of a neuroregulator role of histamine in the CNS; it also presents accumulating evidence suggesting that histamine may be related to circadian rhythmicity in the body.

Key words: histamine, circadian rhythmicity, brain, suprachiasmatic nuclei, pineal gland

INTRODUCTION

During the last two decades, extensive research has been done with the aim of elucidating the role(s) of histamine in various organisms. Hundreds of papers have been published since its synthesis by Windaus and Vogt in 1907 describing the broad distribution of histamine in nature and its diverse biological effects (see Rocha e Silva 1966, 1978, Nowak and Zawilska 1987, Uvnas 1991, Watanabe and Wada 1991). The growing evidence now indicates that the amine plays an important role of a cell-to-cell messenger molecule in many physiological and pathological processes. Major areas of investigations have facussed on histamine's action(s) on, or role(s) in, allergic reactions, gastric acid secretion, cardiovascular system (i.e., cardiac actions, vasoconstruction and vasodilation), and the central nervous system (CNS), including the visual system. All these topics have recently been summarized in several reviews and books (Nowak and Zawilska 1987, Hill 1990, Schwartz et al. 1991, Timmerman and Van der Goot 1991, Uvnas 1991, Wada and Watanabe 1991, Nowak 1991, 1993).

Inspection of the literature covering histamine occurrence, metabolism and receptors (or effects) in various body tissues indicates that only a few studies devoted to histamine in relation to the pineal gland, or to arousal state, were published in the past (Wolf and Monnier 1973, Garbarg et al. 1974, Mezei 1975, Mezei and Mezei 1978). The renewal of interest in establishing the role of histamine in circadian events has coincided with tremendous progress in the field of histamine pharmacology and methodology, as well as in chronobiology, including work on circadian oscillators, the pineal gland and its hormone melatonin, the suprachiasmatic nuclei (SCN), and arousal mechanisms.

In 1992/93 three important observations were reported, which will most likely give a new impetus to research on the relation between histamine and chronobiological events in the body. (1) Mikkelsen et al. (1992) described the existence of histaminergic nerve fibres innervating the pineal gland in rats; (2) Nowak and Sek (1992) showed histamine to be a powerful stimulator of the cAMP generating system in the chick pineal gland; (3) Cote and Harrington (1993) demonstrated the resetting effect of histamine on the circadian clock in the hamster SCN.

This article will survey basic data on histamine in the CNS, and will summarize older and recent findings which suggest an involvement of histamine in circadian rhythmicity, with special emphasis on its role in pineal and/or SCN function.

DISTRIBUTION, LOCALIZATION, AND ORGANIZATION OF THE HISTAMINERGIC NEURONAL SYSTEM IN BRAIN

The occurrence of histamine in animal tissues, including the CNS, has been analyzed with the aid of different techniques, e.g., bioassay (used in early studies), column chromatography followed by spectrophotofluorometric detection, a very sensitive enzymatic radioisotopic assay, or recently introduced highly specific and sensitive HPLC combined with pre- or postcolumn derivatization using *o*-phthalaldehyde, or immunoassay. Using all these methodological approaches, an uneven distribution of histamine in the vertebrate brain has been conclusively established: the highest levels of the cerebral amine in various mammalian species were always reported in the hypothalamus and the lowest in the cerebellum, whereas intermediate values have been found in the thalamus, striatum, hippocampus, and the cerebral cortex (Table I). In addition to highly differentiated content of histamine throughout the brain of the same species, there are marked interspecies differences, especially among lower vertebrates (Table II). Phylogenic studies revealed that histamine is present in the neural tissues of several invertebrates, such as the mollusc *Aplysia*, snail, lobster, crab, and cockroach (see Yamatodani 1991), as well as in insects, where comparatively high quantities of the amine are localized in the visual system (see Nowak 1993).

TABLE I

Histamine levels, L-histidine decarboxylase (HDC) and histamine N-methyltransferase (HMT) activities in the brain of several mammals

		Histamine ng/g wet tissue	HDC dpm/h/g wet tissue ($x10^{-3}$)	HMT dpm/h/g wet tissue ($x10^{-3}$)
Mouse	Cerebral cortex	39.6(6)	49.6(5)	844.6(6)
	Hypothalamus	211.8(5)	393.1(6)	1390.8(6)
	Rest of brain	59.9(6)	163.6(6)	961.0(6)
Rat	Cerebral cortex	50.1(13)	51.7(10)	393.0(10)
	Hypothalamus	318.5(7)	493.1(10)	569.0(10)
	Rest of brain	81.6(10)	184.5(6)	373.2(9)
Chamster	Cerebral cortex	42.5(5)	172.5(6)	964.0(6)
	Hypothalamus	393.3(5)	484.6(5)	1399.8(6)
	Rest of brain	109.2(5)	266.9(6)	1000.0(6)
Guinea pig	Cerebral cortex	41.7(9)	189.1(6)	933.8(6)
	Hypothalamus	292.3(9)	657.6(6)	1410.2(6)
	Rest of brain	73.6(7)	311.0(6)	987.8(6)
Rabbit	Cerebral cortex	74.4(23)	53.5(24)	1057.8(41)
	Hypothalamus	350.7(20)	416.0(29)	1713.0(12)
	Thalamus	132.4(8)	134.2(9)	-
	Caudate nucleus	131.0(6)	71.1(10)	-
	Hippocampus	113.9(6)	62.5(8)	
Cattle	Cerebral cortex	102.3(30)	78.7(6)	796.8(8)
Human	Cerebral cortex	89.7(2)	37.2(2)	768.2(2)
	Hypothalamus	479.0(2)	73.3(2)	1019.4(2)

Results show means from the number of experiments given in parentheses. Results obtained in the author's laboratory. "Rest of brain" refers to the remnants of the whole brain after removal of the cerebral cortex, hypothalamus, cerebellum, pons and medulla oblongata.

The major portion of histamine in an organism is associated with mast cells. It is found in almost all tissues, but notably in heart, lung, and skin. The endothelial cells also store a considerable portion of the body histamine (see, e.g., Gross 1982).

In the CNS, histamine is localized in at least two pharmacologically different compartments, neurones and mast cells (Orr and Pace 1984, Steinbusch and Mulder 1984, Schwartz et al. 1991). The endothelial cells likely represent another storage pool for brain histamine (Gross 1982, Robinson-White and Beaven 1982). A characteristic feature of histamine in neurones, unlike that in the other cellular compartments, is its rapid turnover rate. The half-life of histamine in whole brain, or particular brain areas, was estimated by different approaches giving such extreme values of 30 s (Dismukes and Snyder 1974) and 40-50 min (Pollard et al. 1974), with 20-30 min being most frequently reported (Verdiere et al. 1975, Schwartz et al. 1979, Schayer and Reilly

TABLE II

Histamine levels in brain of some nonmammalian species

		Histamine (ng/g wet tissue)
Aves	Common finch	37.5
	Domestic fowl	94.4
	Adult hen	103.8(6)[a]
	Chick (7-day-old)	
	cerebral hemisphere	75-100[b]
	pineal gland	2025-2700[b]
Reptilia	Lizard	866.8
	Reeves' turtle	877.7
	Blue-green snake	205.7
Amphibia	Bullfrog	294.4
	Newt	412.2
Pisces	Sea bream	9.9
	Horse mackerel	2.6
	Carp	2.9; 49.5(28)[a]
	Goldfish	6.6

Data calculated from Yamatodani (1991), except "a" are from the author's laboratory, and "b" - calculated from Mezei and Mezei (1978).

1983, Oishi et al. 1984). The neuronal amine is intensively synthesized from its amino acid precursor L-histidine, and metabolized mainly by methylation (see below).

The histaminergic neuronal system in the brain has been identified by immunohistochemical methods using, as markers, antibodies directed against the histamine synthesizing enzyme L-histidine decarboxylase (e.g. Tohyama et al. 1991, Wada et al. 1991) and histamine itself (e.g. Panula et al. 1984, Steinbusch and Mulder 1984). Both techniques gave similar results: immunoreactive cell bodies of histaminergic neurones are located exclusively in the posterior basal hypothalamus, i.e., in the tuberal and caudal magnocellular nuclei and postmammillary caudal magnocellular nucleus. The picture is similar in mammals (rat, guinea pig, tree shrew, man), frogs, turtles, and fish (see Wada et al. 1991).

The tuberomammillary neurons extend nerve fibres widely and unevenly, bilaterally, yet with ipsilateral predominance, to various regions of the brain, including the cerebral cortex, caudate-putamen, thalamus, olfactory bulb and tubercle, hippocampus, amygdala, substantia nigra, etc., as shown in Fig. 1.

Recently, a histaminergic projection, originating from the posterior hypothalamus and innervating the pineal gland has been described in rats (Mikkelsen et al. 1992). The histamine-containing fibres innervate the rostral part of the pineal complex, including the deep pineal gland, the pineal stalk and the extreme proximal part of the superficial pineal gland.

BIOSYNTHESIS AND INACTIVATION OF HISTAMINE

Histamine does not readily cross the blood-brain barrier (Neame et al. 1964); this indicates that the

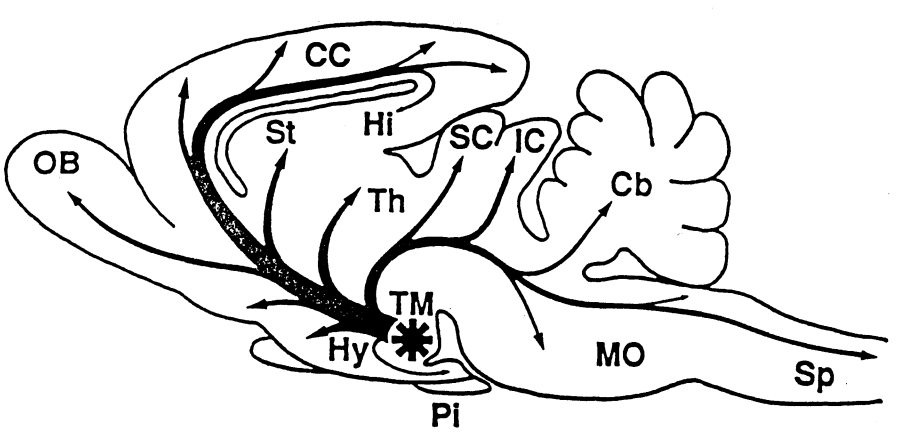

Fig. 1. The histaminergic neuronal system of the rat brain. The cell bodies of the histaminergic neurones are located to the tuberomammillary nucleus (TM) of the hypothalamus (Hy). Arrows indicate the fibre projection (to nearly all brain regions). Abbreviations: OB, olfactory bulb; CC, cerebral cortex; St, striatum; Hi, hippocampus; Th, thalamus; SC, Superior colliculus; IC, inferior colliculus; Pi, pituitary; Cb, cerebellum; MO, medulla oblongata; Sp, spinal cord.

cerebral stores of the amine depend mainly on local biosynthesis (Fig. 2). Histamine biosynthesis involves two steps, first transport of L-histidine into the cell, and second, its decarboxylation by a specific pyridoxal-dependent enzyme, L-histidine decarboxylase (HDC; EC 4.1.1.22).

It has been shown that there is an active, saturable, and energy-dependent transport of L-histidine by brain slices and synaptosomes (e.g. Verdiere et al. 1975, Chudomelka and Murrin 1983). Since the K_m value of L-histidine for HDC (about 0.3-0.45 mM) is somewhat higher than the concentrations of the amino acid in plasma, and presumably, inside neurones (about 60 μM; such concentrations are not sufficient to saturate the enzyme), and L-histidine loading significantly elevates brain histamine (Taylor and Snyder 1972, Nowak et al. 1985), it has been suggested that L-histidine transport may be an important factor controlling histamine formation in the brain.

HDC is unevenly distributed in various regions of the brain, and, similar to histamine levels, its activity is highest in the hypothalamus, followed by the striatum, midbrain, and cerebral cortex. It is lowest in the cerebellum (Table I). Thus, the pattern of distribution of HDC activity throughout the brain

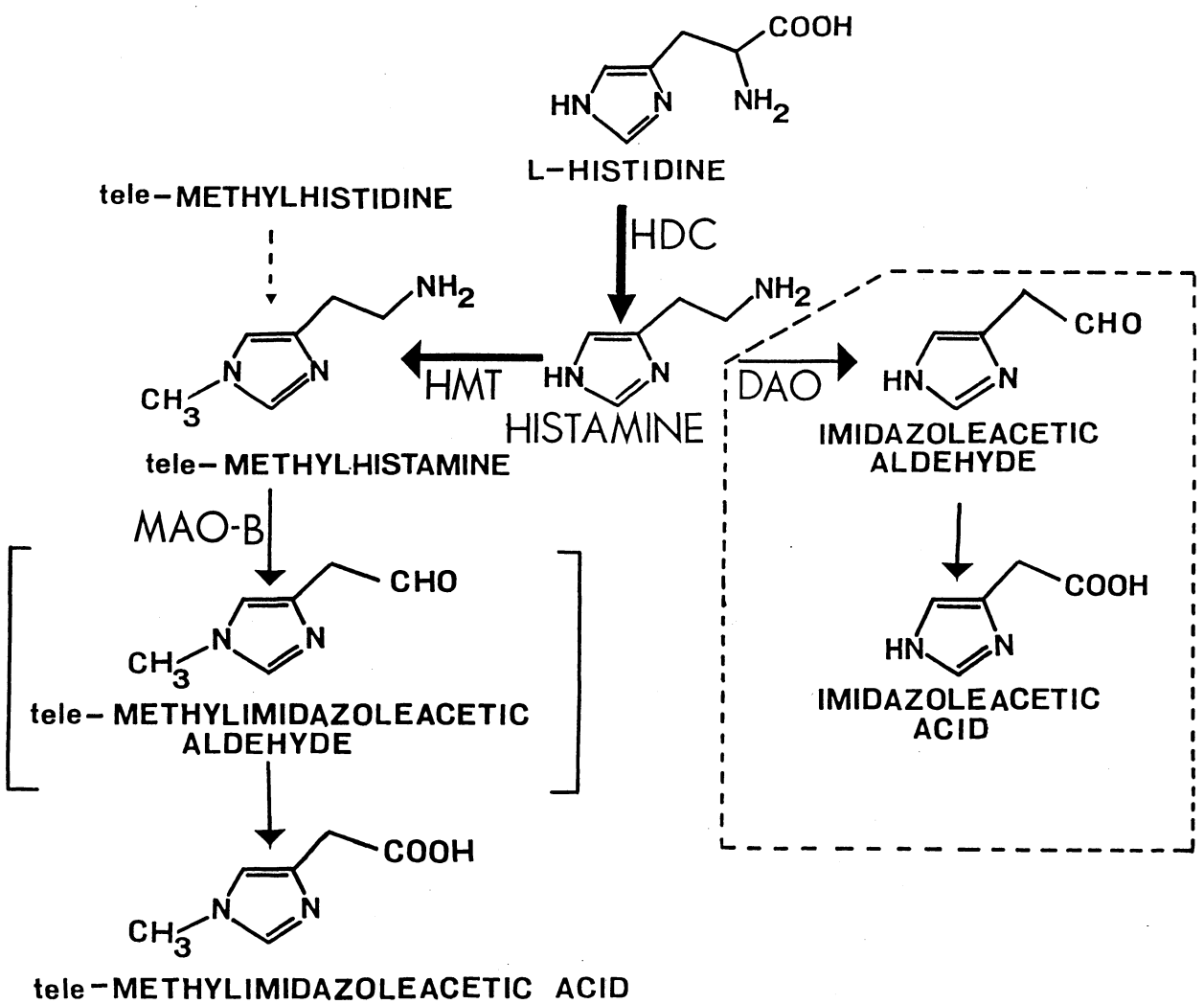

Fig. 2. Main metabolic pathways of histamine in vertebrates. HDC, L-histidine decarboxylase; HMT, histamine N-methyltransferase; MAO-B, monoamine oxidase type B; DAO, diamine oxidase. For other explanations see text.

is consistent with the map of the histaminergic neuronal system in the CNS. The observation that cerebral HDC activity can be recovered, on fractionation of cells, in the P_2 and S (supernatant) fractions (Hegstrand 1985), and in the synaptosomal fraction (which was evidenced by further fractionation of the P_2 fraction; Baudry et al. 1973, Snyder et al. 1974), gives strong support to the idea that histamine - a product of the HDC reaction - plays a neurotransmitter role in the brain.

Unlike monoaminergic neurones in the CNS, which are able to effectively take up monoaminergic neurotransmitters, histamine neurones appear to lack a high-affinity reuptake system that would be responsible for a rapid termination of the amine's biological actions in the brain (snails are probably the exception; Osborne et al. 1979). Therefore, inactivation of brain histamine relies mainly on its metabolism.

In various tissues, histamine catabolism occurs along two alternative pathways (Fig. 2): transmethylation into *tele*-methylhistamine (N^T-methylhistamine), a reaction catalyzed by the enzyme histamine *N*-methyltransferase (HMT; S-adenosylmethionine: histamine *N*-methyltransferase; EC 2.1.1.8), and oxidative deamination into imidazoleacetic acid, catalyzed by diamine oxidase (DAO; histaminase; EC 1.4.3.6). As no DAO activity has been detected in the mammalian CNS, the methylation of imidazole ring *tele*-nitrogen appears to be the main, or even the sole, catabolic pathway for histamine in brains of higher vertebrates. A similar situation seems to exist in the chicken brain, whereas in the carp brain the presence of DAO activity has been reported (Bieganski and Nowak, unpublished); this would mean that in the fish CNS histamine may be catabolized by oxidation.

HMT is present in almost all regions of the CNS, and its activity, unlike the activity of HDC, displays a more even distribution throughout the brain. Experimental data suggest that HMT may be present in both neurones and glia (Garbarg et al. 1974), suggesting a wide-spread enzymatic inactivation of histamine.

Tele-Methylhistamine (N^T-methylhistamine) further undergoes consecutive oxidative deamination with the aid of monoamine oxidase type B (MAO-B; EC 1.4.3.4) and, then, NAD^+-dependent aldehyde dehydrogenase (EC 1.2.1.3), resulting, respectively, in *tele*-methylimidazole acetaldehyde (N^T-methylimidazole acetaladehyde) and *tele*-methylimidazoleacetic acid (N^T-methylimidazoleacetic acid).

There is a possibility that *tele*-methylimidazole acetaldehyde may be metabolized by NADH-dependent aldehyde reductase (EC 1.1.1.1) to an alcoholic product *tele*-methylimidazole ethanol (Schayer 1966). However, the significance of this pathway under physiological conditions remains unclear.

Methylation and oxidation are not the only possible degradative pathways for histamine in body tissues, including the CNS. For example, in the nervous system of snails histamine is metabolized, perhaps exclusively, to the peptide γ-glutamylhistamine (Osborne et al. 1979, Weinreich 1979). The glutamylation of histamine has also been found in the rat brain, where it serves as a minor catabolic route (Konishi and Kakimoto 1976). Moreover, acetylation may be another minor (in mammalian species), or major (e.g., in arthropods) metabolic pathway for histamine in the CNS (Elias and Evans 1983, Sarthy 1991).

HISTAMINE RECEPTORS

Three classes of histamine receptors (termed H_1, H_2, and H_3) have now been identified, the H_3-receptor having been discovered only several years ago. These receptors can be easily distinguished in the CNS by their pharmacology (see Table III), their localization, and the intracellular responses they mediate (see Table IV). The pharmacological and biochemical characteristic of each type of histamine receptor occurring in the CNS is described in detail in several recent reviews (Hill 1990, Fukui 1991, Schwartz et al. 1991a,b), and only a short description of their function will be provided here. It should be added that genes encoding H_1 and H_2 receptors have been cloned (Gantz et al. 1991, Ruat et al. 1991), and the two receptors were expressed and molecularly characterized in several cell lines

TABLE III

Potencies of drugs acting at the three classes of histamine receptors

		Receptor classes		
		H_1	H_2	H_3
Agonist (relative potencies)	Histamine	100	100	100
	2-Methylhistamine	16.5	4.4	<0.08
	4-Methylhistamine	0.23	43	<0.008
	(R)α-Methylhistamine[a]	0.5	1	1,500
	2-Thiazolylethylamine	26	2.2	<0.01
	Dimaprit	<0.0001	71	Antagonist (K_i, 3 μM)
	Impromidine	<0.001	4800	Antagonist (K_i, 65 nM)
Antagonists (K_i values, μM)	Mepyramine (Pyrilamine)	0.0004	-	>0.3
	Cimetidine	450	0.8	33
	Ranitidine	>100	0.2	17
	Tiotidine	>100	0.015	>12
	Zolantidine	6	0.035	>10
	Thioperamide	>100	>10	0.004

Data represent relative agonist potencies, and antagonist activity (K_i values) on biological systems, typical for each class of receptor: H_1 receptor, guinea pig ileum contraction; H_2 receptor, guinea pig atrium rate; H_3 receptor, stimulated histamine release from rat cerebral cortex slices. [a](S) form of α-methylhistamine is a very weak agonist at the H_3 receptor, showing a relative potency of 13.

(Gantz et al. 1991, Yamashita et al. 1991, Traiffort et al. 1992, 1994, Fujimoto et al. 1993).

H_1-Receptors

H_1-Receptors can be specifically labeled reversibly with [^{3}H]mepyramine or [^{125}I]iodobolpyramine, and irreversibly by the photoaffinity probe [^{125}I]iodoazidophenpyramine (see Schwartz et al. 1991). Initial studies indicated that the guinea pig cerebral cortex H_1 receptor is a glycoprotein (Garbarg et al. 1985), and more recent molecular biology approaches have revealed that the mammalian H_1-receptor cDNA encodes a protein of 488-491 amino acids, with a calculated molecular mass (M_r) of 56 kDa (Yamashita et al. 1991, Traiffort et al. 1994).

The stimulation of H_1 receptors increases inositol phospholipid turnover, leads to activation of guanylyl, and in some species adenylyl cyclase, induces glycogen hydrolysis, and triggers arachidonic acid release, possibly via activation of phospholipase A_2. Stimulation of H_1 receptors may also activate the generation of nitric oxide (NO; Leurs et al. 1991). Yet, the common feature of most of these histamine actions is a requirement for intact cells and the presence of Ca^{2+} in the external medium. Therefore, it seems likely that the mobilization of Ca^{2+} is an universal and primary consequence of H_1 receptor activation. In fact, histamine, through interaction with H_1-subclass of receptors, increases intracellular free Ca^{2+} levels in different types of cells (see e.g. Fukui 1991).

It has recently been suggested that H_1-receptors may be coupled to several major signal transduction pathways in a single cell type, as the stimulation of H_1-receptor expressed in CHO cells resulted in (1) an increase in intracellular Ca^{2+}, (2) inositol phosphate mobilization, (3) potentiation of the forskolin-stimulated cAMP accumulation (histamine alone was inactive under basal conditions), and (4) elevation of arachidonate release (Leurs et al. 1994).

TABLE IV

Enzymes or events associated with histamine receptors' activation

Receptor	Activation of enzymes or events	Resulting 2nd messenger (or suspected intermediate)
H_1-receptor	Phospholipase C	IP_3, IP_4 --> Ca^{2+}
		DAG
	NO synthase	[*via* Ca^{2+} (?)]
	Guanylyl cyclase	cGMP [*via* Ca^{2+}, NO (?)]
	Phospholipase A_2	arachidonic acid [via Ca^{2+} (?)]
	Glycogenolysis	[*via* Ca^{2+} (?)]
	Potentiation of cAMP formation	[*via* Ca^{2+}, DAG (?)]
H_2-receptor	Adenylyl cyclase	cAMP
	Phospholipid methylation	
	Inhibition of a Ca^{2+}-dependent K^+ conductance	[*via* cAMP (?)]
	Phospholipase A_2 inhibition	[indirect (?)]
	Phospholipase C (shown in HL-60 cells)	
H_3-receptor	Presynaptic inhibition of:	
	Autoreceptor: release and synthesis of histamine	
	Heteroreceptor: release of serotonin, noradrenaline, acetylcholine (and possibly other neurotransmitters)	

H_2-Receptors

The H_2-receptor molecule is a protein consisting of 358 (rat) or 359 (dog) amino acid residues, with a predicted M_r of approximatelky 40 kDa (Gantz et al. 1991, Ruat et al. 1991).

H_2-receptors can be successfully labeled using [^{125}I]iodoaminopotentidine. Neither [^{3}H]cimetidine, [^{3}H]tiotidine, nor [^{3}H]impromidine appeared to be suitable ligands for specific labeling of this type of receptor (see e.g. Schwartz et al. 1991). The stimulation of H_2-receptors activates both adenylate cyclase in tissue homogenates and cyclic adenosine monophosphate (cAMP) accumulation in intact tissue. However, for unknown reasons, the brain cAMP generating system of the guinea pig and rabbit is much more sensitive to histamine than that of other mammals studied thus far, including rat, mouse, hamster, and monkey. Interestingly, the ability of histamine to stimulate cAMP generation is clearly stronger in slices of the chick brain (Nahorski et al. 1974, 1977), or (particularly) in intact chick or duck pineal gland (Nowak and Sek 1992, 1994a,b), than in pieces of the guinea pig or rabbit brain (Sek et al. 1988, Hill 1990, Schwartz et al. 1991, Nowak 1993). Emerging evidence suggests, however, that the avian cAMP-linked receptor may differ from the mammalian H2-type receptor (see below).

According to recent experimental data, a single H_2-type receptor, expressed in chinese hamster ovary (CHO) cells, is linked not only to activation of adenylyl cyclase, but also to reduction of phospholipase A_2 activity (Traiffort et al. 1992). On the other hand, H_2 receptors on human promyelocytic leukemia (HL-60) cells may be simultaneously coupled to two different cholera toxin-sensitive G-proteins activating adelylyl cyclase and phospholipase C (Mitsuhashi et al. 1989). In addition, the activation of the H_2 receptors can also stimulate phospholipid methylation in the rat CNS (Ozawa et al. 1987, Ozawa and Segawa 1988).

H_3-Receptors

The recent introduction of [^{3}H](R)α-methylhistamine, a highly selective ligand for H_3 receptors (see Table 3), made possible specific labeling of histamine H_3 receptors in the CNS. These receptors are located presynaptically, and when activated, they, as H_3-autoreceptors, regulate stimulated histamine release and synthesis by means of a negative feedback mechanism, and as H_3-heteroreceptors (i.e., receptors localized on nonhistaminergic nerve terminals; Schlicker et al. 1988, 1989, Ichinose and Barnes 1989), inhibit neurotransmitter (e.g., serotonin, noradrenaline, or acetylcholine) release. The mechanism underlying the inhibitory effect of H_3-receptor stimulation on neurotransmitter release in central and peripheral tissues, as well as the molecular characteristics of the H_3-receptor remains to be established.

Other histamine receptors

INTRACELLULAR H_{IC}-HISTAMINE RECEPTORS

Based on their study carried out on microsomal and nuclear fractions of rat liver, Brandes and coworkers (e.g. Brandes et al. 1991) suggested the existence of a novel, intracellular receptor for histamine (named H_{ic}). This receptor (or even receptors), characterized by both high (nM; rat liver nuclei) and low (μM; rat liver nuclei and microsomes) affinity for the amine, was postulated by the authors to mediate various presumed intracellular actions of histamine (e.g., growth promoting activity). However, the evidence presented by Brandes' group seems still insufficient to be considered as a proof of a novel receptor class.

"INVERTEBRATE" HISTAMINE RECEPTORS

A considerable body of evidence has accumulated to suggest that some actions of histamine in invertebrates, particularly in the nervous system of the mollusc *Aplysia* (e.g. Gruol and Weinreich 1979), and in insect photoreceptors (Hardie 1989, Sarthy 1991, see also Nowak 1993), are mediated via receptors coupled to potassium and/or chloride channels. The characteristics of these receptors was different than the characteristics of any known receptor for histamine, thus suggesting, the existence of two "invertebrate" histamine receptors: one of which is a ligand-gated chloride channel (sensitive to strychnine, gallamine, and a number of other nicotinic ligands; Hardie 1989), and the other of which controls the opening of a potassium channel via a pertussis toxin-sensitive G protein (which can be competitively antagonized by cimetidine, but not by other H2-receptor blockers; Gruol and Weinreich 1979).

HISTAMINE FUNCTIONS IN THE CNS

As mentioned earlier, in vertebrates the histaminergic neurones project fibres to almost all parts of the brain. There is also a widespread distribution of histamine receptors throughout the brain. In accordance with this, many diverse effects of histamine in or on CNS tissues have so far been described, suggesting that the histaminergic neuronal system may participate in the regulation of various activities of the brain (see e.g. Nowak and Zawilska 1987, Hill 1990, Schwartz et al. 1991, Timmerman and Van der Goot 1991, Uvnas 1991, Watanabe and Wada 1991). Thus, briefly, histamine may control processes, phenomena and systems in the CNS such as: (1) arousal state, (2) energy metabolism, (3) different forms of behaviour, (4) neuroendocrine system, (5) autonomic function, and (6) analgesia. In addition, histamine seems to play the role of neuromodulator in the retina, as well as in some other ocular elements, e.g., the uvea (see Nowak 1993). It is possible that some effects of histamine may result not only from its action on neurones, but also on glial cells (Arbones et al. 1988, Inagaki et al. 1991, Kubo et al. 1991) and blood vessels (Gross 1982).

HISTAMINE AND CIRCADIAN RHYTHMS IN AN ORGANISM

All living organisms (including plants, animals and man) have adjusted to the 24-h period of the natural environment so as to be prepared for efficient activity during either the daytime or at night. Because of this, almost all of an organism's structures and functions undergo regular 24-h (i.e., circadian) changes.

It has been suggested that the vertebrate circadian system is controlled from a number of anatomically distinct structures, of which the retina, the hypothalamic suprachiasmatic nuclei (SCN) or its homologue (the visual suprachiasmatic nuclei in the chick; Cassone et al. 1990), and the pineal gland, are the most important constituents. The relative importance of these three components varies considerably between different animals, and, depending on the species, each may function as a self-sufficient circadian oscillator (Deguchi 1979, Moore 1983, Besharse et al. 1988, Takahashi et al. 1989, Underwood et al. 1990, Klein et al. 1991). The mechanisms underlying self-sustaining activity of a "biological clock" are not fully understood, and the term "black box" was frequently used for many years to embrace those mysterious events of the CNS which are regulated by environmental input signals, such as light:dark cycle and/or temperature changes, and also in some cases behavioural or social factors. These environmental signals are time cues capable of entraining (synchronizing) an endogenous pacemaker, which, under constant conditions, shows a persistent periodical activity, driving diverse overt rhythmic variables.

A great number of central neurotransmitters are likely involved in the control of rhythmic events in an organism (Van der Pol and Tsujimoto 1985, Medanic and Gillette 1992, Shibata and Moore 1993). In this respect, histamine has received less attention than monoamines, excitatory amino acids, or neuropeptides. It has to be recalled, however, that more than two decades ago Monnier and collegues (1970) observed an electroencephalogram desynchronization in rabbits following intracerebroventricular administration of histamine. Based on the results of their early electrophysiological experiments, these authors suggested histamine was an arousal factor in mammals (Monnier et al. 1970, Wolf and Monnier 1973). Subsequent studies, carried out on rats and cats by different authors, fully supported the "histamine arousal hypothesis" (Kiyono et al. 1985, Monti et al. 1985, Reiner and McGeer 1987, Lin et al. 1988, 1990, Wada et al. 1991), indicating that, in fact, histamine may be related to rhythmic activity of the brain.

Recent studies are very suggestive of such a role for histamine. For example, it has been shown that an increase in histaminergic activity in the brain (achieved by intracerebral injection of histamine during the early subjective dark period) produced a permanent delay of the circadian phase of locomotor or drinking activity in rats maintained on a 12:12 hours light:dark illumination cycle (Itowi et al. 1990). Biochemical "microdialysis" experiments showed the existence of a clear circadian variation in the histamine release from the hypothalamus of freely moving rats kept under a 12:12 hours light:dark cycle (Mochizuki et al. 1992). The pattern of this circadian variation in histamine release (with high values during the dark phase, and low values during the light phase), running in parallel with daily pattern of locomotor activity (Mochizuki et al. 1992), suggested that the activity of the central histaminergic system is correlated with the circadian rhythm of rats. Since diurnal fluctuations in brain histamine content (and/or metabolism) were reported to occur not only in rats (hypothalamus - Orr and Quay 1975, Schwartz et al. 1975, pineal gland - Garbarg et al. 1974), but also in other animal species, including rabbit, rhesus monkey, mouse, and guinea pig (Tuomisto and Tuomisto 1982, Oishi et al. 1987, Nowak and Socko 1988, Nowak et al. 1988, Prell et al. 1989, Nowak 1991, Tuomisto 1991), it seems reasonable to consider histamine as one of several neuromodulators playing a role in circadian rhythmicity. Thus, an intriguing question is which region of the brain serves as an anatomical substrate for the described histamine action? There are several possibilities, and some will be discussed below.

HISTAMINE AND THE SUPRACHIASMATIC NUCLEI (SCN)

The SCN of the anterior hypothalamus perform a primary pacemaking function for circadian rhythms in mammals (Moore 1983, Meijer and Rietveld 1989, Klein et al. 1991). In birds and lower vertebrates, whose pineal glands are directly photosensitive and possess independent biological oscillators (cf. Takahashi et al. 1989), these nuclei do not seem to be essential for the rhythmic pineal activity (Cassone et al. 1990), being however of crucial importance in maintaining other circadian rhythmicities (see e.g., Cassone 1991).

The intrinsic pacemaking properties of the mammalian nuclei were demonstrated when the SCN were surgically isolated from the animal and cultured using the hypothalamic brain slice technique (Shibata et al. 1982, Gilette 1986). Using such methodology, the effects of iontophoretically- or bath-applied histamine on spontaneous electrical activity of the SCN neurones have been studied. Thus, in rats, histamine evoked both mepyramine-sensitive inhibition and mepyramine-sensitive augmentation of neuronal activity. The proportion of the particular responses varied in different studies. Liou et al. (1983) reported mainly inhibitory responses (in 34% cells vs 17% "excitatory" responses), whereas Stehle (1991) observed mainly excitatory responses (45% vs. 10% "inhibitory" responses). In the latter study, the histamine-evoked excitatory responses were independent of the circadian time, thus, suggesting that histamine does not play a pivotal role in generation and maintenance of circadian rhythm.

However, in another *in vitro* electrophysiological study, Cote and Harrington (1993) reported that in hamster hypothalamic slices containing SCN, histamine reset the circadian clock in a manner similar to light, and that the resetting effect of histamine is mediated via H_1 receptor since co-application of mepyramine antagonizes the response to the amine.

Evidently, more study is needed to clarify the nature of the action of histamine on SCN neurones. Such a need is highlighted by two additional mammalian observations: (1) there is a rich histaminergic innervation of the SCN by fibres originating in the hypothalamic tuberomammillary nucleus (to which histamine-containing cell bodies are restricted; Panula et al. 1984, Tokyama et al. 1991), and (2) the SCN region is characterized by very high content of histamine (6.3 ng/mg protein - Brownstein et al. 1974, or 690 ng/g tissue - Pollard et al. 1976).

HISTAMINE AND THE PINEAL GLAND

The pineal gland is closely involved in rhythmic functions of the body, and its hormone melatonin exhibits a distinct circadian rhythm (Reiter 1991, Zawilska and Wawrocka 1993). To the author's knowledge, there is very little literature dealing with histamine and the pineal gland. The existing data are limited to only a few species. Nevertheless, all relevant papers reported the presence of histamine in the vertebrate pineal gland. There are large differences between animal species in pineal histamine concentrations, due probably to differences in mast cell numbers (Machado et al. 1965). Some species like the goat or the chick have very high histamine contents in the pineal gland, while much lower levels, close to mean brain values, are found in the pig (Tuomisto 1991) or the rat (see below). The rat and the chick pineal glands have received more attention from histaminologists, and those histamine data will be discussed in detail.

Rat

Using sensitive radioenzymatic assay, the histamine content of the rat pineal gland was estimated to be in the range of 50-60 pg/gland (Garbarg et al. 1974). The activities of histamine synthesizing and inactivating enzymes, HDC and HMT, respectively, showed levels either only slightly above blank values (HDC; Garbarg et al. 1974), or non-measurable ones (HMT; Backstrom and Wetterberg 1972). However, in rats maintained on a 12:12 hours light:dark illumination cycle, histamine levels displayed a clear-cut daily rhythm, with the highest

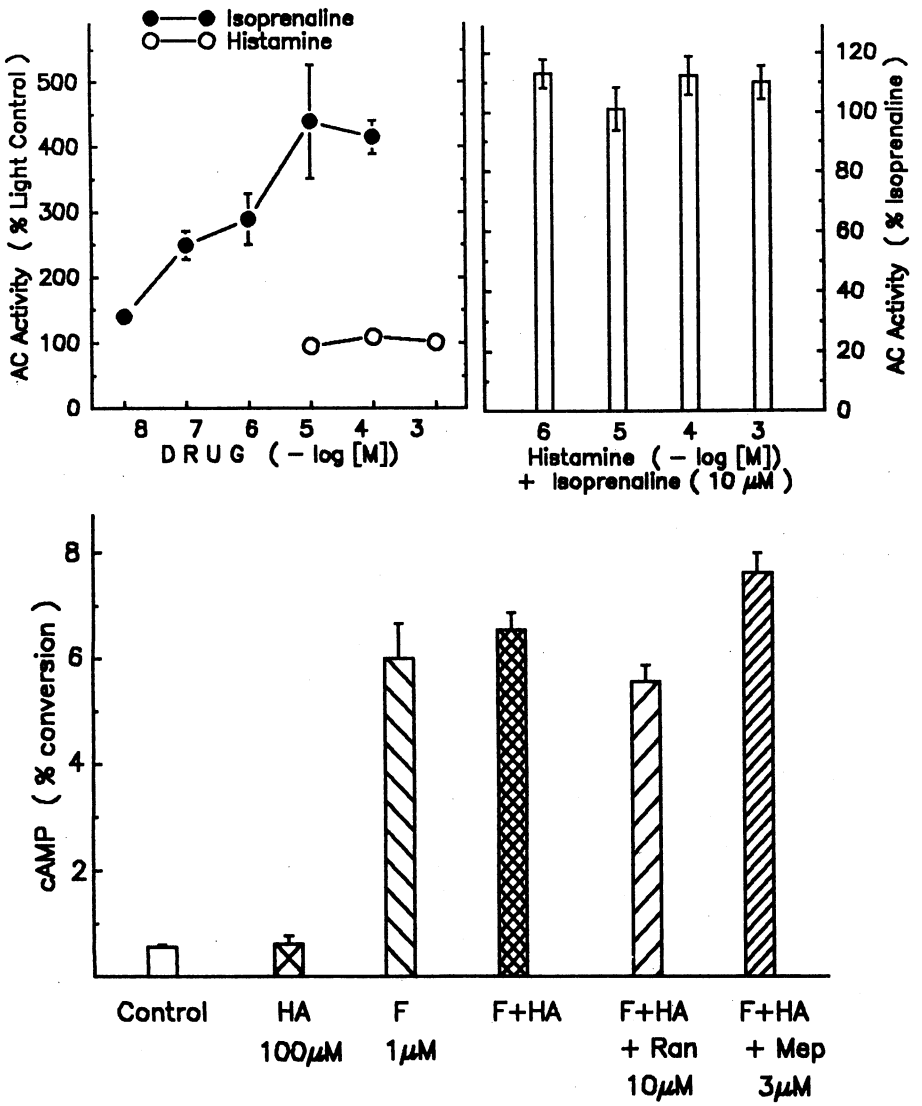

Fig. 3. Effect of histamine on basal and stimulated cAMP generating system of the rat pineal gland. Top left, adenylyl cyclase (AC) basal activity; Top right, isoprenaline (10 μM)-stimulated adenylyl cyclase (AC) activity. Bottom, basal and forskolin (F; 1 μM)-stimulated cAMP formation in intact [^{3}H]adenine-prelabelled glands: effect of histamine (HA; 100 μM) alone, or in combination with ranitidine (Ran) and mepyramine (Mep). Results represent means SEM (n = 4-14).

values occurring at the beginning of the dark period. There was a 2-fold difference between the light period and the dark period; Garbarg et al. 1974).

An immunohistochemical study revealed that histaminergic nerve fibres originating from the posterior hypothalamus project to the rat pineal complex (Mikkelsen et al. 1992), suggesting that a histamine signal may affect pineal function. Yet, our recent *in vitro* experiments have shown that in rats histamine influenced neither the activity of adenylyl cyclase in pineal homogenate, nor cAMP accumulation in intact glands, under both basal and forskolin-stimulated conditions (Fig. 3; Nowak and Sek 1994). Moreover, histamine applied in a wide range of concentrations did not significantly modify the ability of isoproterenol to stimulate *in vitro* activity of adenylyl cyclase (Fig. 3), or *ex vivo* activity of serotonin N-acetyltransferase, the key regulatory enzyme in the melatonin biosynthetic pathway.

Loading of rats with L-histidine (a procedure that effectively elevates the endogenous histamine content in the brain; Fig. 4), or with selective blockers of histamine H_1- and H_2-receptors, alone or in combination, had no significant effect on the pineal NAT activity, measured under light and dark conditions (Fig. 4).

In conclusion, in the rat pineal gland which receives histaminergic neuronal input, histamine does not seem to regulate biosynthesis of either cAMP or

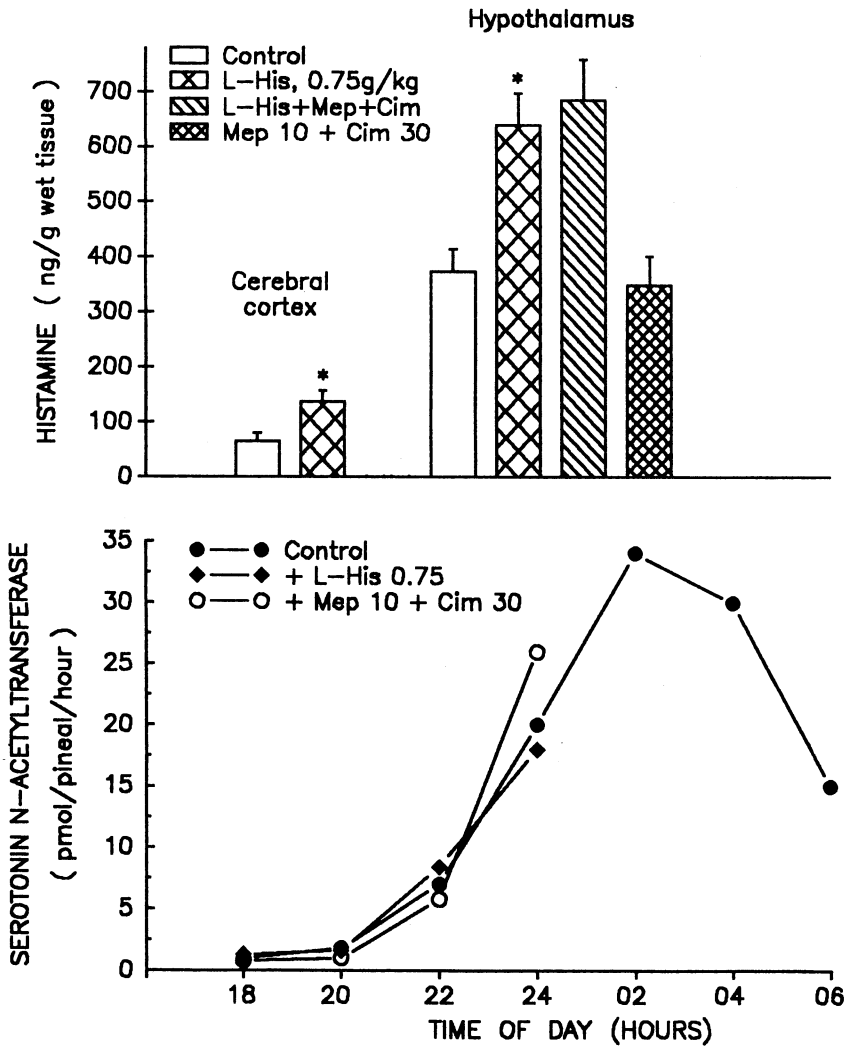

Fig. 4. Effect of L-histidine (L-His) loading (0.75 g/kg; 90 min) and combination of mepyramine (Mep; 10 mg/kg) and cimetidine (Cim; 30 mg/kg) on (Top) histamine content in the cerebral cortex and hypothalamus, and (Bottom) ex vivo nocturnal serotonin N-acetyltransferase activity in the pineal gland of the rat (rats maintained on a 12:12 hours light:dark illumination cycle, with lights off between 18.00-06.00).

the main pineal hormone melatonin, and therefore its role in the function of this organ remains unknown.

Chick

Two papers by Mezei (1975, 1978) described the presence of both histamine and HMT activity in the chick pineal gland. Developmental analysis of these two parameters revealed that in the 13-15-day embryo histamine levels and HMT activity are very low; thereafter, until hatching, both values rose rapidly, reaching the highest levels on the day of hatching for HMT or 2-5 days after hatching for histamine.

To the author's knowledge, there have been no immunohistochemical studies of the presence of histaminergic fibres innervating the chick pineal gland. However, such innervation seems likely to exist, since histamine exerts a powerful action on the pineal gland activity.

Histamine and the cAMP generating system of the chick pineal gland

In 1992 we demonstrated for the first time that histamine dose-dependently stimulated cAMP formation in intact [^{3}H]-adenine prelabelled pineal glands, taken from 2-3-week old chicks. That had been maintained from the day of hatching on a 12:12 hours light: dark illumination cycle, and killed at the end of the light phase (Fig. 5; Nowak and Sek 1992).

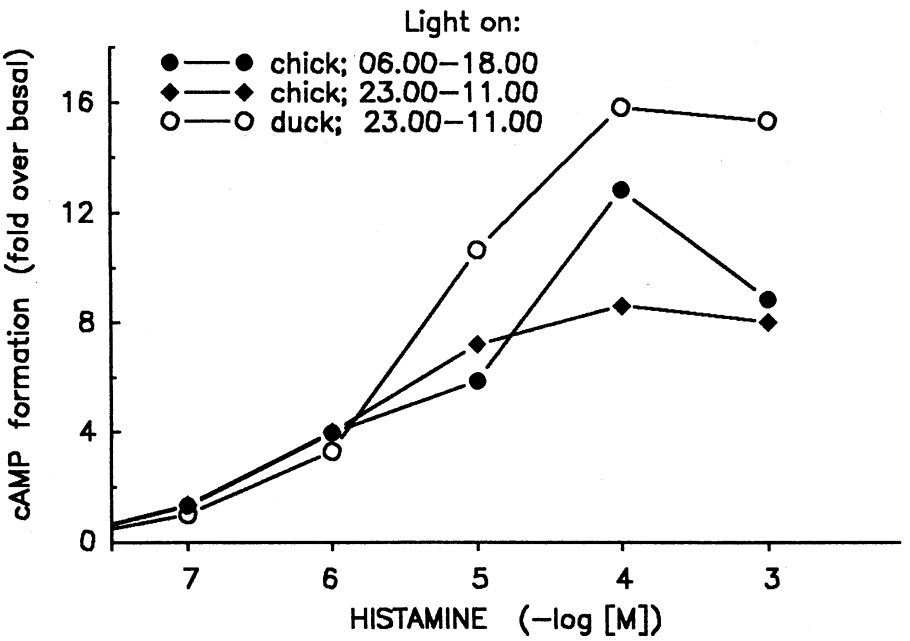

Fig. 5. *In vitro* effect of histamine on cAMP formation in intact [^{3}H]adenine-prelabeled pineal glands of 2-3-week-old chicks and ducks. The pineal glands were isolated always between 10.00-10.30; the animals were maintained on a 12:12 hours light:dark illumination cycle. Note that the chick experiments were performed at two different times relative to light:dark cycle.

These unexpected preliminary data encouraged us to thoroughly analyse the action of histamine on the vertebrate pineal gland. In addition, this histamine effect appeared interesting in a broader aspect since it was clearly stronger than the histamine action in cerebral cortex slices or sections of chick retina (Nahorski et al. 1974, 1977, Nowak and Sek 1991, Nowak 1993), as well as in the brain of guinea pig or rabbit (Sek et al. 1988; see also Hill 1990, Schwartz et al. 1991, Nowak 1993). There are also findings suggesting the role for histamine in the mechanisms underlying circadian rhythmicity in various animal species, and, as mentioned earlier, the pineal gland is an important component of the circadian system.

After careful pharmacological analysis of histamine action, carried out with a number of selective agonists and antagonists of histamine H_1-, H_2-, and H_3-receptors, we reached the conclusion that the histamine effect in the chick pineal gland is specific, and receptor-mediated, and that the receptor involved in this histamine action does not represent any currently known histamine receptor subtype. Since the histamine-evoked stimulation of cAMP formation in the chick pineal gland was antagonized non-competetively only by H_2-blockers, we suggested that, according to mammalian criteria, the pineal receptor may represent an avian-specific H_2-like receptor (Nowak and Sek 1992, 1994a,b,c). However, the results of our latest experiments performed on the duck organ (Fig. 5) strongly suggest that there may be a novel histamine receptor subtype present in avian pineal, because the stimulatory effect of histamine on pineal cAMP production was resistant not only to H_1- and H_3-receptor selective antagonists, but also to ranitidine - a potent H_2-receptor blocker. Therefore, in the chick and duck pineal gland, histamine potently stimulates cAMP production, and this effect is mediated through a receptor whose pharmacology is not consistent with the pharmacological characteristic of either H_1-, H_2-, or H_3-receptor types, thus, suggesting an involvement of a novel histamine receptor subtype.

It is pertinent to mention that addition of histamine to organ-cultured chick pineal glands in the middle of the light phase (incubation with histamine continued in darkness) dramatically increased the endogenous cAMP level and significantly enhanced NAT activity in the gland (Voisin, personal communication; Matczak and Nowak, unpublished data).

Thus, based on the data cited above, it seems very likely that histamine may play the role of a

physiological regulator of pineal activity in birds. The question, however, still remains open as to whether histamine conveys any information from the brain to the pineal gland, or the simply serves as a local modulator in the gland.

CONCLUDING REMARKS

Accumulating biochemical and neurochemical evidence strongly suggests that histamine, a central neurotransmitter and/or neuromodulator, is involved in many functions that exhibit circadian rhythms. The way in which histamine affects the rhythmic phenomena in the body may vary in different animal species. The amine may change the activity of some brain nuclei that control circadian rhythmicity, such as the SCN in mammals, or it may influence the function of the pineal gland, as for instance in birds. There is also a possibility that the amine might modulate some rhythmic events via ocular mechanisms since histamine in the eye may be involved in the transmission/processing of visual signals (see Nowak 1991, 1993); this may apply particularly to mammals, in which information about the light-dark cycle (the most important entrainer of rhythmic functions) is obtained via the eyes and the retinohypothalamic tract to the SCN.

Work over the last several years has provided an increasing number of impressive observations relating histamine to arousal mechanisms and circadian rhythmicity; however, their revelance for understanding the basic physiology requires much more research.

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