Polish Journal of Pharmacology
Pol. J. Pharmacol., 2004, 56, 407–413
ISSN 1230-6002

PERTUSSIS TOXIN-SENSITIVE G PROTEIN MODULATES THE ABILITY OF HISTAMINE TO STIMULATE cAMP PRODUCTION IN THE CHICK PINEAL GLAND

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Pertussis toxin-sensitive G protein modulates the ability of histamine to stimulate cAMP production in the chick pineal gland. J.B. ZAWILSKA, J. ROSIAK, J.Z. NOWAK. Pol. J. Pharmacol. 2004, 56, 407–413.

Histamine (HA) is a potent stimulator of cAMP synthesis in various structures of chick brain, including the pineal gland. The action of HA is mediated by specific, membrane bound H_2-like receptors, whose pharmacological profile is different from that described for H_2-receptors in mammalian tissues. In this work, we analyzed the effects of cholera toxin (CTX) and pertussis toxin (PTX), well-known modulators of G_s and G_i/G_o protein, respectively, on the stimulatory action of HA on cAMP synthesis in the chick pineal gland organ cultures. HA and its two biologically active methylated derivatives, 2-methylHA and 4-methylHA, markedly increased cAMP content in the chick pineal glands. Pretreatment of the chick pineal glands with CTX potently stimulated basal cAMP production. In CTX-pretreated glands, elevations of cAMP synthesis evoked by HA, 2-methylHA and 4-methylHA were additive to those produced by CTX, which is an observation suggesting that H_2-like HA receptors in the chicken pineal gland are not coupled to G_s proteins. Pretreatment of the chick pineal glands with PTX significantly enhanced the stimulatory effect of HA and, to a greater extent, 2-methylHA on cAMP production. The enhancing action of PTX on the HA-evoked cAMP formation was not modified by mepyramine, a selective H_1-type HA receptor antagonist. It is suggested that in the chick pineal gland, a population of HA receptors is coupled to G_i (or G_o) protein. Stimulation of these receptors would tonically suppress the activity of the cAMP generating system functionally linked to H_2-like HA receptors.

Key words: *histamine receptors, chick, pineal gland, cAMP, G proteins, cholera toxin, pertussis toxin*

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INTRODUCTION

The autacoid and neurotransmitter/neuromodulator histamine (HA) is an important regulator of a wide variety of cellular functions (for reviews see [2, 6, 9, 15, 20]). HA exerts its numerous biological actions through activation of specific, membrane-bound receptors. Based on pharmacological and molecular cloning studies, HA receptors have been classified into four different subtypes, termed H_1, H_2, H_3, and H_4; all of them are members of a superfamily of G protein-coupled receptors (GPCR) (e.g. [9, 11, 12, 16, 26]). Among various activities ascribed to HA, its ability to stimulate cAMP formation was repeatedly demonstrated in different tissues and species [9, 11], including the central nervous system (CNS) of guinea pig, rabbit, and chicken [1, 19, 21, 27]. The HA-evoked increase in cAMP formation usually results from activation of the H_2-type HA receptor. However, in some species, a H_2-receptor-mediated effect can be enhanced by a concomitant stimulation of H_1 receptors [7]. We have previously demonstrated that HA is a powerful stimulator of cAMP production in the cerebral cortex of young cocks [31, 34], and in intact pineal glands of domestic fowls, i.e. hen, duck, and goose. HA, however, did not affect the nucleotide formation in the rat pineal gland [22–25]. The stimulatory action of HA on cAMP formation in the avian brain was mediated by a specific receptor, whose pharmacological profile is different from that of the H_1-, H_2-, H_3-, and H_4-subtypes of HA receptors described for mammalian tissues. It has been suggested that this HA receptor represents either an avian-specific H_2-like receptor or a novel HA receptor subtype [22–24, 34]. Nature of the molecular mechanism(s) underlying HA action on cAMP formation is unknown, because HA appears to be a weak stimulator of adenylyl cyclase activity in membrane preparations of the chick pineal gland (as well as those of the chick cerebral cortex), although in parallel experiments the amine nicely stimulated the enzyme activity in membranes of guinea pig cerebrum [31, 32, 34]. It has been hypothesized that a primary, relatively weak signal originating from stimulation of H_2-like HA receptors is potentiated by a concomitant activation by HA of another intracellular signaling pathway(s). In order to shed more light on this problem, we analyzed the effects of cholera toxin and pertussis toxin, well-known modulators of activity of G_s and G_i/G_o proteins, respectively [3], on the stimulatory effect of HA on cAMP synthesis in the chick pineal gland organ cultures.

MATERIALS and METHODS

Chemicals

Histamine-2HCl (HA) was purchased from Serva (Heidelberg, Germany). 2-Methylhistamine-2HCl (2-methylHA) and 4-methylhistamine-2HCl (4-methylHA) were kindly donated by Prof. R.C. Ganellin and Prof. M.E. Parsons (SmithKline & Beecham, Hertz, UK). Dulbecco's phosphate buffered saline (DPBS), 3-isobutyl-1-methylxanthine (IBMX), cholera toxin (CTX), mepyramine (pyrilamine maleate), and pertussis toxin (PTX) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Cyclic AMP radioimmunoassay kit (TRK-432) was from Amersham Pharmacia Biotech UK Ltd. (Buckinghamshire, UK). Other chemicals were of analytical purity and were purchased from commercial sources. All drug solutions were prepared immediately before use.

Animals

Male white leghorn chicks (*Gallus domesticus*, HyLine) were purchased locally on the day of hatching, and kept in temperature-controlled warmed brooders (29 ± 1°C during the first 5 days and at 26 ± 1°C afterward) with standard food and tap water available *ad libitum*. The animals were entrained to a 12 h light : 12 h dark illumination cycle (LD; lights on at 8:00) for a minimum of one week prior to the study. The lighting cycle was produced by overhead cool fluorescent lamps providing light intensity at the level of the animals' heads of approximately 150 lux. The chicks were killed by decapitation (always between 9:00 and 9:30), their pineal glands were quickly isolated, washed twice in ice-cold DPBS, and used for further biochemical studies. The experiments were carried out in strict accordance with the Polish governmental regulations concerning experiments on animals (Dz.U.97.111.724).

Chick pineal gland organ cultures

Pineal glands were cultured individually in 0.5 ml DPBS (gassed with 95% O_2:5% CO_2), at 37°C, for 24 h under the LD schedule. Next morn-

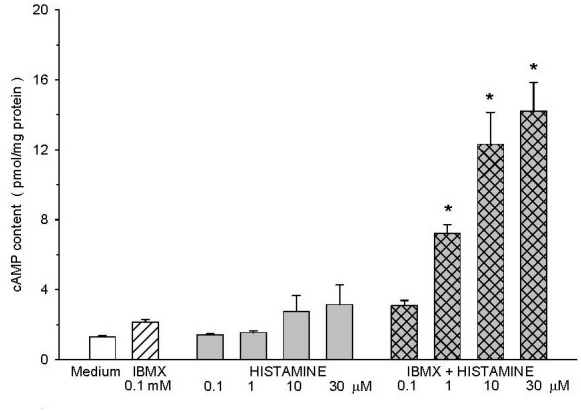

Fig. 1. Effects of histamine (0.1–30 μM) on cyclic AMP content in the chick pineal gland organ cultures. The action of histamine was tested in the absence and presence of 0.1 mM IBMX in the incubation medium; n = 6–10 pineal glands/group. *p < 0.05 *vs.* IBMX

ing, the culture medium was replaced by the fresh, gassed DPBS with or without 0.1 mM IBMX. Following 5 min, HA, 2-methylHA or 4-methylHA were added, and the incubation was continued (under light) for the next 10 min. At the end of an experiment, pineal glands were quickly frozen in liquid nitrogen. Pineal glands were individually homogenized in ice-cold 50 mM Tris HCl buffer (containing 4 mM EDTA; pH 7.5), in a proportion of one pineal/80 μl. The homogenate was boiled for 3 min, cooled in an ice bath, and then centrifuged at 10,000 × *g* for 2 min at 4°C; 50 μl aliquots of the resulting supernatant were used for measurement of cAMP content. Cyclic AMP was measured by radioimmunoassay, with the aid of the commercially available kit (TRK-432; Amersham-Pharmacia-Biotech). Protein content was determined by the method of Lowry et al. [17], using bovine serum albumin as a standard.

Toxin pretreatment

Chick pineal glands were preincubated with either pertussis toxin (150 ng/ml) for 16 h, or with cholera toxin (1 μg/ml) for 2 h, before determination of the effect of the tested drugs on cAMP content.

Data analysis

Data are expressed as the means ± SEM, and were analyzed for statistical significance by ANOVA followed by *post hoc* Student-Newman-Keuls' test.

RESULTS

HA (0.1–30 μM) potently increased, in a concentration-dependent manner, cAMP contents in the cultured chick pineal glands. The effect of HA required the presence of IBMX in the incubation medium. IBMX used at a 0.1 mM concentration significantly elevated the basal cAMP content in the chick pineal glands. Incubation of the pineal

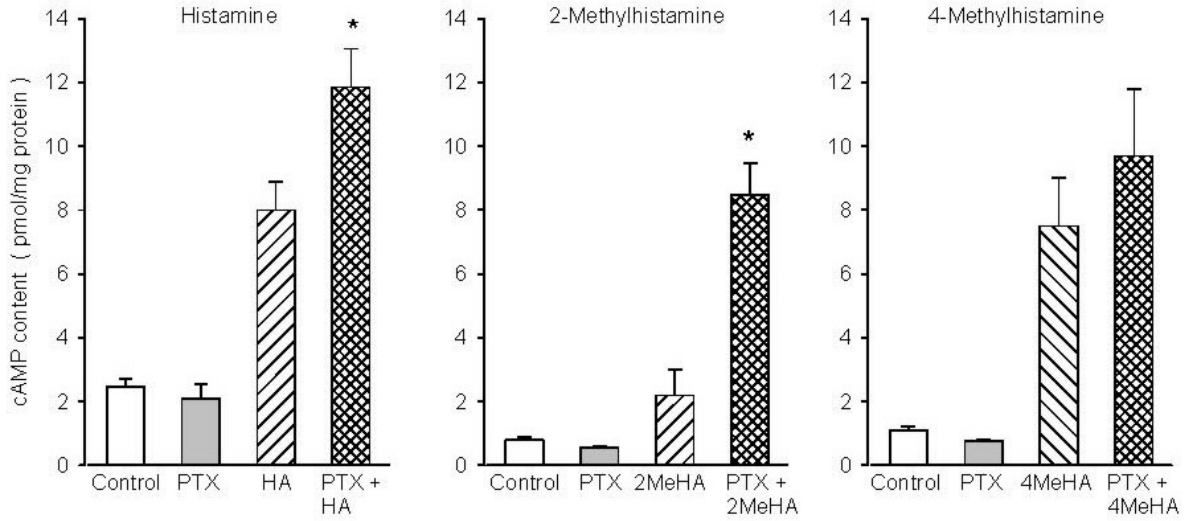

Fig. 2. Effect of pertussis toxin (PTX) on the stimulatory action of histamine (HA, 1 μM), 2-methylhistamine (2MeHA, 100 μM) and 4-methylhistamine (4MeHA, 100 μM) on cAMP content in the chick pineal gland organ cultures. The incubation was carried out in the presence of 0.1 mM IBMX; n = 10–15 pineal glands/group. *p < 0.05 *vs.* HA or 2MeHA

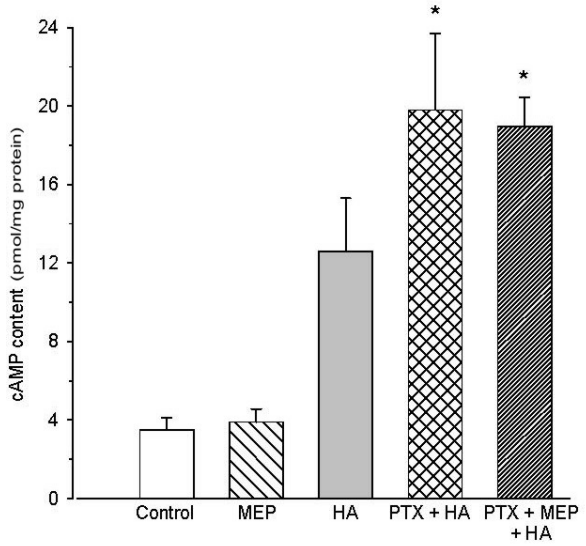

Fig. 3. Effect of mepyramine (MEP, 3 μM) on HA (1 μM)-evoked increase in cAMP content in the chick pineal gland organ cultures pretreated with pertussis toxin (PTX, 150 ng/ml). The incubation was carried out in the presence of 0.1 mM IBMX; n = 3–4 pineal glands/group. *p < 0.05 *vs.* HA

glands with IBMX and HA resulted in 1.5-fold (0.1 μM HA), 5-fold (1 μM), 10-fold (10 μM) and 12-fold (30 μM) increase in tissue cAMP level (Fig. 1). The stimulatory action of HA on cAMP production in the cultured chick pineal glands was mimicked by 4-methylHA and, to a lower extent, by 2-methylHA (Fig. 2).

Pretreatment of chick pineal glands with PTX (150 ng/ml, 16 h) significantly enhanced the stimulatory effect of HA (1 μM) and 2-methylHA (100 μM) on cAMP production (Fig. 2). In PTX-pretreated pineal glands, the increase in cAMP content evoked by 100 μM 4-methylHA was higher (by 32%) than the increase observed in the control glands, non treated with the toxin. This difference did not, however, reach the level of statistical significance (Fig. 2). Mepyramine, a selective antagonist of H_1-HA receptor, did not modify the effect of 1 μM HA on the cAMP level in pineal glands incubated in the presence of 0.1 mM IBMX and pretreated with PTX (Fig. 3).

Incubation of chick pineal glands for 2 h with CTX (1 μg/ml) potently increased the tissue cAMP content (Fig. 4 and 5). In the chick pineal gland organ cultures pretreated with 1 μg/ml of CTX, the stimulatory effects of HA (1–30 μM; Fig. 4), 2-methylHA and 4-methylHA (used at 100 μM; Fig. 5) on cAMP concentrations were significantly higher than those observed in the non-treated glands. An analysis of the studied interaction between CTX and HA, 2-methylHA or 4-methylHA revealed its additive character.

DISCUSSION

As outlined in the Introduction, stimulation of H_2-HA receptors leads to an increase in cAMP formation in a number of systems [1, 4, 7, 13, 16, 21–25, 27, 30–32, 34]. A considerable body of experimental data indicate that the capability of HA to stimulate cAMP production results from the H_2-receptor-mediated activation of adenylyl cyclase *via* a guanine nucleotide-dependent mechanism [4, 5, 13, 30, 34]. Activation of H_2-HA receptor has also been associated with other signal transduction events, such as, for example, stimulation of phospholipid methylation [28], inhibition of Cl^--mediated K^+ conductance [8], inhibition of phospholipase A_2 activity [29], and stimulation of phospholipase C activity [14, 30], IP_3 formation [33], and mobilization of intracellular Ca^{2+} [5, 18]. However, at least in mammals, the activation of phospholipase C-linked signaling system, with concomitant formation of IP_3 and diacylglycerol (DAG) as second messengers, usually results from stimulation of the H_1-HA receptor [10, 16].

Our earlier studies carried out on the pineal gland and cerebral cortex of several avian species, including chick, suggested that HA stimulated cAMP synthesis by acting on a receptor resembling to a certain extent the mammalian H_2 type receptor. The pharmacological profile of this receptor is, however, markedly different from that described for a classical mammalian H_2-HA receptor (see Introduction; also [22, 23, 31, 32, 34]). For example, the rank order of potency of several HAergic compounds to stimulate cAMP production in the two chick tissues was atypical in terms of the involved receptors: HA ($H_1 = H_2 = H_3$) ≥ 4-methylHA (H_2) ≥ Nα,Nα-dimethylHA (H_2,H_3 > H_1) > 2-methylHA (H_1) > amthamine (H_2) > 2-thiazolylethylamine (H_1) > dimaprit (H_2) ≈ Rα-methylHA (H_3) > *tele*-methylHA (inactive). Furthermore, the HA-, as well as 4-methylHA- or 2-methylHA-evoked cAMP responses were antagonized by selective H_2-receptor blockers, and were not affected by H_1- or H_3-antagonists.

In order to further characterize the HA signaling pathway(s) in the avian brain, the effects of PTX

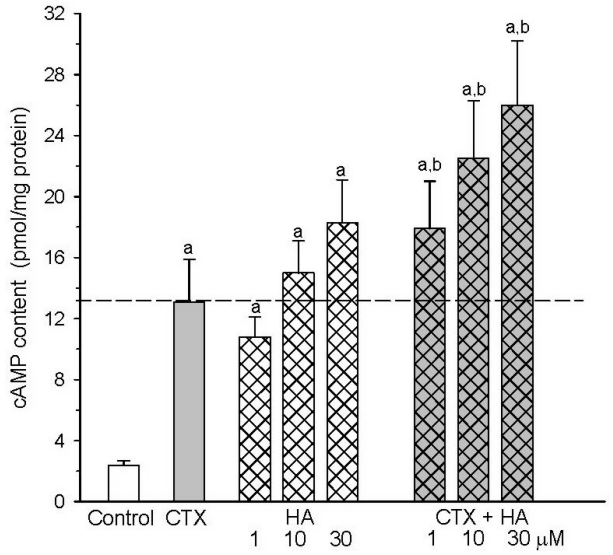

Fig. 4. Effect of cholera toxin (CTX, 1 μg/ml) on an increase in cAMP content evoked by histamine (HA, 1–30 μM). The incubation was carried out in the presence of 0.1 mM IBMX; n = 6–12 pineal glands/group. $^{a}p < 0.05$ *vs.* control, $^{b}p < 0.05$ *vs*. HA

and CTX on the stimulatory action of HA on cAMP synthesis in the chick pineal gland organ cultures were analyzed. PTX (also known as the islet activating protein) is a bacterial toxin produced by certain *Bordetella pertussis* strains. PTX ADP-ribosylates G_i and G_o proteins, leading to functional uncoupling of these proteins from receptors [3]. Thus, sensitivity to PTX can serve as an indication of the involvement of G_i/G_o protein in a signal transduction pathway. CTX, a secretory product of *Vibrio cholerae*, is commonly used as a modulator of G_s protein activity. The toxin ADP-ribosylates $G_{S\alpha}$, an active subunit of the G protein associated with activation of adenylyl cyclase and generation of cAMP. CTX-catalyzed ADP-ribosylation inhibits the intrinsic GTP-ase activity of $G_S\alpha$, thereby prolonging its active state. This, in turn, leads to a prolonged activation of adenylyl cyclase by G_S [3].

In agreement with earlier reports [22, 23, 25], HA and two of its biologically active methylated derivatives, i.e. 2-methylHA and 4-methylHA, selective agonists (according to the mammalian criteria) of H_1- and H_2-HA receptors, respectively, potently increased cAMP contents in the chick pineal gland organ cultures. In the current study we have found that treatment with PTX effectively enhanced the stimulatory action of HA and, to a greater extent, 2-methylHA on cAMP levels in the chick pineal glands. These data are suggestive of a coupling of HA receptor in the chick pineal gland to G_i protein. On the contrary, in experiments performed on cloned human H_2 receptors it has been demonstrated that the HA-induced cAMP generation is insensitive to PTX, which suggests that members of the G_i/G_o family of G proteins were not involved in the studied HA signaling [5, 14, 30]. As 2-methylHA preferentially activates H_1-HA receptors (at least in mammalian systems), a possible role of the H_1-type receptor-stimulated pathway as a mechanism underlying the PTX-evoked effects reported here should also be considered. In order to address this question, experiments with mepyramine, a selective blocker of H_1-HA receptor, were performed. In line with earlier observations [22–24, 34], mepyramine did not modify the stimulatory action of HA on cAMP level in the pineal gland. Furthermore, the HA-induced increase in cAMP content in the glands pretreated with PTX was unaffected by mepyramine, thus weakening the role of H_1-receptors in the studied process.

In another set of experiments, we analyzed the influence of CTX on the H_2-like receptor-dependent stimulation of cAMP synthesis in the chick pineal gland organ cultures. The observed additive effect of CTX and HA, 2-methylHA, or 4-methylHA on cyclic AMP contents in the pineal gland of chick suggests that the HA receptor, stimulation of which leads to activation of cyclic AMP-generating system in this tissue, is not coupled to G_s protein. Consistent with this hypothesis, HA weakly and only when used at high, milimolar, concentration stimulated adenylyl cyclase activity in membrane preparations of the chick pineal gland [32]. In contrast to the chicken, several studies have demonstrated that in mammals the stimulatory action of HA on cAMP production involves activation of H_2-HA receptors coupled through G_s protein to adenylyl cyclase [4, 5, 13, 30].

The potency of HA to stimulate cAMP synthesis in the chick pineal gland organ cultures (present results, [22, 23, 25, 32]) and slices of chick cerebral cortex [34] is in contrast to its weak action on adenylyl cyclase activity in membranes prepared from these two tissues [25, 32, 34]. This observation led us to hypothesize that a primary, relatively weak signal originating from stimulation of the H_2-like HA receptors (i.e. H_2-like receptor $\rightarrow$ adenylyl cyclase), is potentiated by a concomitant activation by HA of another intracellular signaling

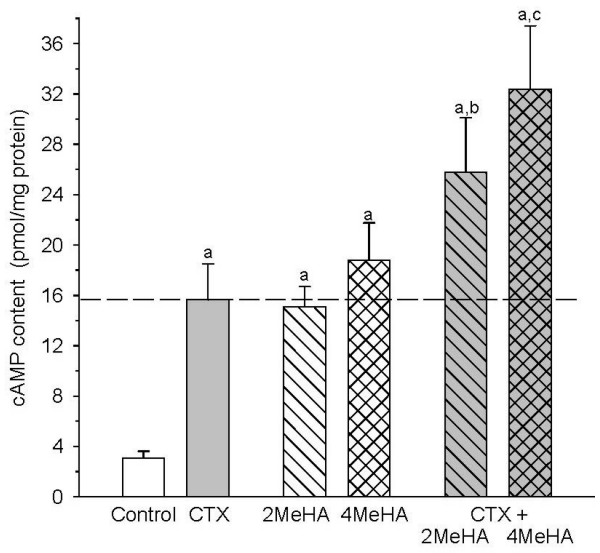

Fig. 5. Effect of cholera toxin (CTX, 1 μg/ml) on an increase in cAMP content evoked by 2-methylhistamine (2MeHA, 100 μM) and 4-methylhistamine (4MeHA, 100 μM) in the chick pineal gland organ cultures. The incubation was carried out in the presence of 0.1 mM IBMX; n = 4–6 pineal glands/group. $^{a}p < 0.05$ *vs.* control, $^{b}p < 0.05$ *vs.* 2MeHA, $^{c}p < 0.05$ *vs.* 4MeHA

pathway(s) [31, 32, 34]. One of likely candidates of such a pathway is: HA receptor → G_q/G_{11} protein (insensitive to pertussis toxin) → phospholipase C → IP_3/Ca^{2+}, DAG → protein kinase C. Two lines of evidence seem to support this suggestion. Firstly, the HA-evoked rise in cAMP formation in the chick pineal gland and cerebral cortex was significantly reduced by selective inhibitors of protein kinase C, suggesting an important role of this enzyme in the HA-triggered cascade of biochemical events leading to a large stimulation of cAMP production in avian CNS [31, 32]. Furthermore, HA effectively increased the accumulation of inositol phosphates in the chick tissues [32, 33]; this HA action was sensitive to the H_2-blocker [32]. It should be noted that human H_2 receptors, in addition to H_1-type receptors, can activate phospholipase C and rise the intracellular free Ca^{2+} concentration in different models [9, 16], by a mechanism involving activation of G_q/G_{11} protein [5, 14, 30].

In summary, this report shows that the treatment of the chick pineal gland organ cultures with PTX, which inactivates G_i and/or G_o protein, enhances the ability of HA to stimulate cAMP production. Such a phenomenon would result from the elimination by this toxin of a tonic adenylyl cyclase activity-suppressing HA-receptor-derived signal operating in the chick pineal under physiological conditions. It remains to be established, whether in the avian CNS such a PTX-sensitive signal originates from the HA-stimulated intracellular signaling pathway (cross-talk between HA-driven two messengers' pathways simultaneously stimulated by activation of the avian-specific H_2-like receptor; a possible role of the H_1-HA receptor-linked phospholipase C pathway has been eliminated by the results of the present experiments with the H_1-blocker mepyramine), or it results from a non-HA receptor-linked signaling which physiologically affects the HA-sensitive cyclic AMP generating system (cross-talk between two signaling pathways linked to two different neurotransmitter receptors). Finally, the observation that G_s protein plays a marginal role in the HA-dependent cAMP production in the chick pineal gland provides an additional support to our hypothesis, originally based on results of pharmacological studies, that H_2-like HA receptors in birds markedly differ from the receptors described for mammals.

Acknowledgments. This study was supported by the grants No 4 PO5A 104 from the State Committee for Scientific Research, Warszawa, Poland, and No 502-13-856 from the Medical University of Łódź.

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Received: March 10, 2004; in revised form: June 16, 2004.