fore, it is important to examine further the taste receptor potential with an abrupt waveform of gustatory stimulation. To do this a nozzle of the gustatory stimulator was put 100–400 μm away from the microelectrode tip and 0.5 *M* NaCl was applied at the rate of 0.04 ml/sec. In successful cases, where intracellular recording was not disturbed, receptor potentials showing much shorter rise times were obtained. The upper trace of Figure 3 shows an example where the rise time was approximately 200 msec. In 17 investigated taste cells the rise time was in the range of 50–360 msec (mean ± SE, 160 ± 30 msec) and no phasic component was observed. In these experiments, an adapting Ringer solution was not flowed before the application of test 0.5 *M* NaCl solution. As shown in the lower trace of Figure 3, the concentration change of the onset of 0.5 *M* NaCl application was almost rectangular in form, which was measured as the junction potential between the microelectrode tip located on the papilla surface and the flowing 0.5 *M* NaCl.

It has been predicted that the taste receptor potential may possess an obvious initial phasic response when the rate of taste stimulus onset is steep and that the initial transient discharge in the gustatory nerve is caused by the phasic receptor potential[10,11]. This assumption probably must be discarded, however, because the present experiment done with the rapid rise of taste stimulus onset still could not exhibit any phasic component of receptor potential.

Histamine-Induced Hypotension Modified by H_1 and H_2 Antagonists in the Monkey (*Macaca mulatta*)

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Summary. Blocking H_2 receptors with burimamide in the dose used (20 mg/kg) approximately doubles the amount of histamine needed to produce the same effect as seen when H_1 antagonists (chlorpheniramine or mepyramine) are used alone. The K_z ratios for chlorpheniramine-chlorpheniramine plus burimamide are 117–204 and for mepyramine-mepyramine phus burimamide are 200–478. H_1 and H_2 receptors, in the monkey, when stimulated, both cause cardiovascular responses in the same direction.

There are two types of histamine receptors[2], the H_1 receptors which are blocked by the classical 'mepyramine-like' antihistamines and the H_2 receptors which are insensitive to this group of antihistamines. Even large doses of H_1 antagonists do not completely block the hypotensive effects of histamine.

In the cat, H_1 and H_2 receptors both act in the same direction to lower blood pressure[3]. However, in the calf, some of the H_2 receptors modulate the depressor effect of H_1 receptor stimulation, the two receptors acting in opposite directions[4].

Burimamide, a thiourea analogue of histamine, which seems to be a specific antagonist of the H_2 receptors, was introduced in 1972[3]. The present study was undertaken to determine the hypotensive response of monkeys to histamine and the extent and direction to which the H_1 antagonists chlorpheniramine and mepyramine and the H_2 antagonist burimamide affect this response.

Materials and methods. The animals used in this study were young, healthy *Macaca mulatta*, weighing 3.0–3.5 kg. Injections were made through a femoral venous catheter, and blood pressure measurements were made with a catheter inserted into the femoral artery. Prior to each test, each animal was anesthetized with an i.v. injection of sodium Nembutal (35 mg/kg). Each animal was then given a series of histamine injections of gradually increasing concentration from 0.025 to 100 μg/kg. After each dose of histamine, changes in blood pressure were measured as the maximum decrease of mean arterial pressure. Each animal's blood pressure was allowed to recover to normal between doses which were given at least 10 min apart.

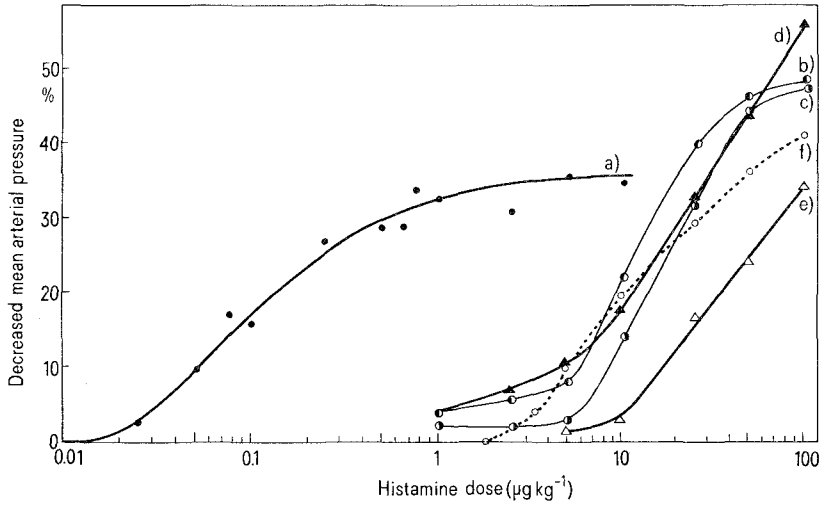

Fig. 1. Effect of histamine antagonists on histamine-induced vasodilation in the monkey. a) Histamine alone; b) after chlorpheniramine; c) after chlorpheniramine and burimamide; d) after mepyramine; e) after mepyramine and burimamide; f) after phenoxybenzamine.

Computed characteristics associated with double reciprocal dose-response plot of histamine with and without antagonists

	Maximal response (Δ *max*), %	One-half maximal response ($^1/_2 \Delta$ *max*), %	Dose at $^1/_2 \Delta$ *max* (K_X), µg/kg	K_Z ratio (K_X agonist + antagonist) / (K_X agonist)
Agonist				
Histamine alone	37	18.5	0.115	
Antagonists				
Chlorpheniramine (10 mg/kg)	56	28	13.5	117
Chlorpheniramine (10 mg/kg) and burimamide (20 mg/kg)	62	31	23.5	204
Mepyramine (10 mg/kg)	63	31.5	23	200
Mepyramine (10 mg/kg) and burimamide (20 mg/kg)	53	26.5	55	478
Phenoxybenzamine (2 mg/kg)	47	23.5	12.5	110

Seven animals were then injected with chlorpheniramine[5] (10 mg/kg), an H_1 antagonist, and the histamine injections repeated. Another 7 animals were injected with mepyramine[6] (10 mg/kg), an H_1 antagonist, and the histamine injections repeated. 8 animals were given a combination of chlorpheniramine (10 mg/kg) and burimamide[7] (20 mg/kg), an H_2 antagonist, before the histamine injections. 7 other animals were given a combination of mepyramine (10 mg/kg) and burimamide (20 mg/kg) before the histamine injections. The chlorpheniramine and mepyramine were in 10 ml of isotonic saline. The burimamide (10 mg/ml of water) was buffered to a pH of 7.2 and infused over a 10 min period because of its hypotonicity.

Three animals were given an α-adrenergic blocking agent, phenoxybenzamine[8] (2 mg/kg), 1 h before a series of 12 histamine injections in graded doses from 0.14 to 100 µg/kg to determine the effect of adrenergic stimulation by histamine on maximal response.

Results and discussion. The response to exogenous histamine is graphically depicted in Figure 1.

One method of comparing the efficacy of antagonists is by first determining the effective dose at the middle of the dose response curve, i.e., one-half maximum response[9–11]. By using a double reciprocal plot, the value of the maximal response can be derived from responses elicited by physiological concentrations of the agonist.

A double reciprocal plot of the data can be seen in Figure 2. Using the data from Figure 1 (with the exception of the responses less than 10%, having variation coefficients (SD/x) close to unity), straight lines were fitted by the least squares method. Using the notation of GOLDSTEIN et al.[11], the equations associated with these lines can be written in the usual linear fromat of $y = a + bx$:

$$\frac{1}{\Delta} = \frac{1}{\Delta\, max} + \frac{K_x}{\Delta\, max} \cdot \frac{1}{x} \qquad (1)$$

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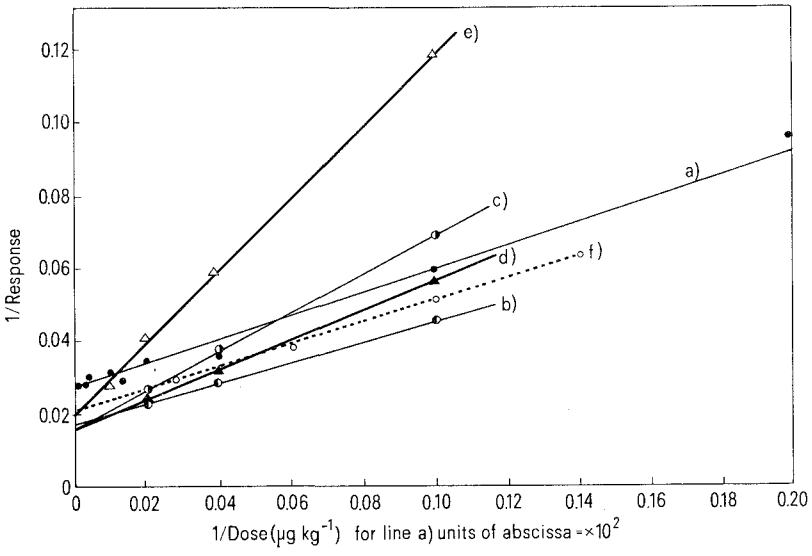

Fig. 2. Double reciprocal dose-response plot of histamine with and without antagonists. a) – f) see Fig. 1.

where A is the biological response (percent decreased mean arterial pressure), $Amax$ is the maximal response, x is the concentration of histamine (μg/kg), and K_x is the dissociation constant. In this instance, K_x is also the concentration of histamine needed to produce one-half the maximum response. The intercept in equation (1) is $1/Amax$, which provides the value of maximal response from which one-half the maximum response is calculated. The concentration K_x at which the one-half maximum response occurs can also be obtained from the least squares solution to equation (1) by simple algebraic manipulation. K_x is the dose ratio of the concentrations of agonist needed in the presence and absence of antagonist to produce the same response. Theoretically, for competitive antagonism, the doseresponse curves with and without antagonists should be parallel and of equal heigh or maximal response[9,10]. The response in vivo, however, is complicated by the interaction of different physiological systems, resulting in this instance in increased maximal response after antagonism.

The maximal responses to histamine after antogonism do not differ significantly from each other but do differ significantly from the maximal response when histamine is given alone (Table). This would seem to indicate that some factor is present which modulates the effect of the agonist and is absent after the antagonists are given.

One explanation for this may be based on the stimulating effect of histamine on the adrenal medulla causing the liberation of catecholamines with their characteristic pressor effects[12,13]. The response to histamine would thus be a summation of pressor and depressor effects. The release of catecholamines by histamine is abolished by antihistamines; this could result in the increased maximal response after antihistamines are given. To test this possibility, 3 monkeys were given an α-adrenergic blocking agent (phenozybenzamine, 2 mg/kg) which would presumably block any modulating effect of catecholamines on the maximal response. After this treatment, the maximal effect was increased to 47%, providing a possible explanation for the discrepancy (Figure 1).

Although the Lineweaver-Burke method is an excellent means of determining the maximal response of an agonist, the value of the dissociation constant, when based on blood pressure presponses, is of lesser accuracy. The concentration of the drug in contact with receptors may be different from the concentration in the circulating blood which is a reflection of the concentration of the injectant. The changes in blood pressure reflect a composite of changes in the entire cardiovascular system[9]. The dissociation constant between a drug and its receptors may be different in different tissue, hence the dissociation constant determined from in vivo data must be viewed with these factors in mind.

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Regional Variations of Choline-Acetyltransferase in the Chick Embryo Optic Lobe

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Summary. The specific activity of CAT and AChE was determined in different regions of the chick embryo optic lobe at several stages of development. Regional differences in CAT activity appeared in 9-day-old tectum, being the postero-basal area the one with higher enzymatic activity. On the other hand, at 6th and 13th day of development, the levels of AChE and CAT are similar throughout the optic lobe.

The avian optic tectum is an excellent model to study the pattern of development of a nervous center and the effect of peripheral innervation upon its differentiation. A sizable body of literature, gathered in the last few years[2-4], has provided insight into the major features of its development. Thus, it is known that several phases of cell proliferation and migration are involved in the organization of its precise laminated structure so that, by the 12th day of development, all the main strata of the mature tectum are recognizable. At every stage its antero-latero-ventral portion is further developed than the caudo-dorso-medial region.

The optic nerve, which is the main afferent connection of the tectum, reaches its antero-ventral base around the 6th day of development and progressively invades the tectal surface in an antero-ventral (AV) to postero-dorsal (PD) sequence, paralleling the gradient of morphological differentiation and cell proliferation. Between days 12 and 13 of development the growing front of the optic fibres has invaded all parts of the tectum including its postero-dorsal surface[5].

The present study analyzes whether the AV-PD wave of cytoarchitectonic differentiation and of sequential ingrowth of retinal fibres across the tectal surface is also paralleled by a differential enzymatic activity of the neural cells. For this purpose, the activity of the enzymes of the cholinergic system, choline acetyltransferase (CAT) and acetylcholinesterase (AChE) was determined in different regions of the optic lobe at several stages of development.

Materials and methods. Eggs from a fertile stock of White Leghorns were incubated at 37 °C. When the embryos reached the desired stage of development, they were removed from the shell and washed several times with Hanks saline solution.

Since the optic lobe undergoes a rotation of 90° between days 7 and 13 of development[5,6], it is extremely important to define the coordinates used to isolate the different regions. In the 6-day-old embryo, the tectum

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