containing ^{14}C-histamine plus various concentrations of burimamide. The muscles were then washed for 10 minutes.

Mast cells of the HC line (Furth mastocytoma) were grown in the ascitic form in the LAF_1 mice (Jackson memorial Laboratory). Cells were removed at an appropriate phase of tumour growth by aspiration of the peritoneal fluid, centrifuged and resuspended in a medium containing ^{14}C-histamine, and ^{14}C-histamine plus different concentrations of burimamide. Following 1 hour incubation (gas phase: air; pH 7.4; 37°C) cells were counted, harvested washed three times and extracted.

Cardiac tissues and mast cells were homogenized in 0.4 N perchloric acid and suitable aliquots were taken for total radioactivity, histamine, and methyl-histamine assay. Total radioactivity was measured in the perchloric acid extract, using a liquid scintillation counter (Packard Tri Carb, 3314); histamine was determined by isotopie dilution method [3], and methyl-histamine was assayed according to SNYDER, AXELROD and BAUER [4]. In mast cells, assay by the BSH method showed that ^{14}C-histamine accounted for all radioactivity; therefore, in further experiments the isotope dilution procedure was no longer necessary, and the amount of radioactive material found in perchloric extracts was directly referred to ^{14}C-histamine.

Results and Discussion

Results are summarized in the figure. At all the concentrations studied on the isolated atrium, burimamide clearly prevents both the accumulation of total radioactivity and the formation of methyl-histamine; the uptake of the unchanged amine was not significantly affected.

In mouse mast cells, burimamide simply blocks the accumulation of histamine; the $I.D._{50}$ for total radioactivity was much lower in the mast cells than in the atrium.

These data support the hypothesis that, beside the action at H_2-receptor sites in guinea pig atria burimamide is provided of inhibitory effects on the histamine methylating systems, while it is capable of blocking the histamine storage in mouse neoplastic mast cells.

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Utilization of Endogenous ATP During Histamine Release from Isolated Rat Mast Cells

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The stimulus exerted by anaphylactic reactions, compound 48/80, and extracellular ATP on isolated rat mast cells depends on a functioning intracellular ATP production to lead to the secretion of histamine. In contrast, *n*-decylamine and chlorpromazine release histamine from mast cells, irrespective of the presence of inhibitors or energy metabolism [1]. However, how the cellular ATP is linked to the mechanism of histamine release induced by the energy-dependent histamine releasing agents is so far unknown. On the one hand, it has been proposed [2] that endogenous ATP is not utilized during the secretion but is of importance to maintain the cells in a responsive state. On the other hand, from equal lack of direct experimental data an active utilization of endogenous ATP during the release has been postulated [3]. It was pointed out by DIAMANT and FREDHOLM [4] that 'the final proof will depend on correlations between histamine release from mast cells and their content and turnover of energy-rich phosphate bonds'. The present investigation aims for such final proof.

After the addition of antimycin A (0.2 μM) to suspensions of isolated rat mast cells the ATP content gradually decreased to one third of the original value within 2–3 minutes. Concomitantly, the cells lost their ability to release histamine when exposed to 48/80. The addition of glucose (0.2–0.6 mM) to cells preincubated for 3 minutes with antimycin A partially restored ATP to a

steady state level within 2.5 minutes. Concomitantly, the ability of the cells to release histamine when exposed to 48/80 was restored.

In order to investigate if the energy dependence of 48/80-induced histamine release reflected an increased utilization of the mast cells during histamine release, the ATP content of mast cells was determined immediately before and 20 seconds after the addition of 48/80. Using cells with an intact energy production no effect on the ATP content was found after the addition of 48/80 although histamine release had occurred. However, when cells were preincubated with antimycin A for 1 minute to stop oxidative generation of ATP, the decrease of the ATP content was significantly greater after histamine release had been induced by 48/80 than in control samples without 48/80. In contrast, when corresponding experiments were performed with chlorpromazine and *n*-decylamine, the ATP content in samples where histamine release had been induced did not differ from that in control samples neither in the presence nor in the absence of antimycin A.

Our experiments indicate that histamine release induced by 48/80 but not that induced by chlorpromazine or *n*-decylamine is accompanied by an increased utilization of endogenous ATP. A decrease in ATP content escaped detection in mast cells which maintain intact metabolic pathways, probably due to a fast regeneration of the ATP utilized.

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Modifications of Brain HA Metabolism Induced by Antihistamines

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Most of antihistamines are known to possess central actions which mechanism is not well understood. We have checked whether antihistamines could modify histamine (HA) metabolism in rat brain.

For this purpose, the endogenous store of histamine was labelled by intraventricular administration of high activity ^{3}H-histidine (^{3}H-His). ^{3}H-His, ^{3}H-HA and ^{3}H-methylhistamine (MHA) its main catabolite [1] were specifically assayed. Peak values for ^{3}H-HA and ^{3}H-MHA were observed at about 1 hour. The cross-over of the specific activities curves occured, as could be expected for a precursor-product relationship, at the maximum of the HA specific activity. We have chosen to study the effects of antihistamines on HA utilization, with minor interference of amine synthesis. Therefore they are given, intraperitoneally, 1 hour after ^{3}H-His; the animals were killed 3 hours later. Since the specific activity of His was less than 10% of the HA one after 90 minutes, one may think that during the 3 hours period of drug action, synthesis of ^{3}H-HA was very small compared to its utilization. Several antihistamines of different chemical structures were tested. At 50 mg/kg, promethazine, brompheniramine, dexchlorpheniramine and also selective antagonists of H_1- and H_2-receptors (mepyramine and burimamide respectively) [2] induce an important increase of ^{3}H-MHA concentration (38–110%) and a lesser one of ^{3}H-HA (20–58%). When dexchlorpheniramine, the most potent in both effects was tested at lower dosages (2 or 10 mg/kg), only the ^{3}H-MHA elevation was still present (11–28%), ^{3}H-HA being unchanged (in fact no significantly decrease). These findings suggest that antihistamines modify brain HA metabolism by two different mechanisms possibly related to two different properties already known of these drugs:

(a) they increase HA turnover as a result of blockade of central histaminergic receptors;

(b) they decrease HA inactivation by inhibition of Histamine-N-methyltransferase (HMT).

Blockade of central HA receptors by standard antihistamines is well known from electrophysiological studies [3].