Proposed Mode of Action of Histamine

SUTHERLAND and his collaborators have firmly established that the cyclic nucleotide, adenosine 3′,5′-monophosphate (CAMP), is a ubiquitous regulator of a variety of intracellular processes[1]. Its role in the activation of phosphorylase has been elucidated by Sutherland and Rall[2]. It is now almost certain that CAMP also participates in the activation of lipase in adipose tissue[3], and may affect the activity of such key regulator enzymes as phosphofructokinase[4,5]. Furthermore, CAMP has been implicated as the intracellular mediator of a variety of hormonal effects ranging from steroidogenesis in the corpus luteum and adrenal cortex to increased water permeability in toad bladder and kidney tubules[1].

CAMP is formed in cells by the enzymatic cleavage of adenosine triphosphate (ATP) through the action of the enzyme known trivially as adenyl cyclase. The enzyme cyclic nucleotide phosphodiesterase breaks down CAMP to adenosine 5′-phosphate. Studies with the purified enzyme revealed that methyl xanthines such as caffeine and theophylline inhibit diesterase, and that imidazole activates it[6]. In studies on the regulation of lipolysis in adipose tissue, I have found that theophylline increases lipolysis, and that imidazole (10 mg/ml.) inhibits epinephrine-stimulated lipolysis (unpublished work). These studies suggest that even within intact cells, phosphodiesterase is responsive to the actions of these drugs.

Imidazole differs from histamine only in the respect that histamine contains an aminoethyl side-chain. To test the possibility that histamine also activates phosphodiesterase in adipose tissue, segments of parametrial fat were excised from female albino rats and incubated *in vitro* in the presence of 0·05 μg/ml. of adrenaline chloride (Parke, Davis and Co.) and histamine dihydrochloride (Calbiochemicals). The tissues were incubated for 1 h in 1 ml. of Krebs–Ringer bicarbonate buffer containing 40 mg/ml. of bovine serum albumin (Armour, Fraction V), 1 mg/ml. of glucose and 0·1 mg/ml. of ascorbic acid. Glycerol produced from the hydrolysis of triglycerides and released into the medium was measured by the enzyme procedure of Weiland[7]. The results are shown in Table 1. Adrenaline caused a four-fold increase in the production of glycerol. This lipolytic effect was virtually abolished by the addition of 10 mg/ml. of histamine dihydrochloride to the medium.

Table 1. EFFECTS OF HISTAMINE AND EPINEPHRINE ON LIPOLYSIS IN ADIPOSE TISSUE

	Glycerol release (μmoles/g/h)
Experiment 1	
Control	1·63 ± 0·35*
Histamine (10 mg/ml.)	1·89 ± 0·21
Adrenaline (0·05 μg/ml.)	6·64 ± 1·01†
Adrenaline + histamine (10 mg/ml.)	2·65 ± 0·30‡
Adrenaline + histamine (1 mg/ml.)	5·85 ± 0·37
Experiment 2§	
Control	1·38 ± 0·24
Dibutyryl CAMP (0·6 μg/ml.)	5·83 ± 0·52†
Dibutyryl CAMP + histamine (10 mg/ml.)	3·82 ± 0·38¶

* Mean ± *S.E.M.* 6 observations/group.

† Significant increase ($P < 0·001$).

‡ Significantly different from epinephrine alone ($P < 0·01$), but not from control ($P > 0·05$).

§ Eight observations/group.

¶ Significantly different from dibutyryl CAMP alone ($P < 0·01$) and significantly different from control.

In a separate experiment, performed with epididymal fat from male rats, histamine reduced the lipolytic effect of the dibutyryl analogue of CAMP (Calbiochem) by about half. Dibutyryl CAMP is a more effective lipolytic agent than the natural cyclic nucleotide allegedly because it penetrates cell membranes more readily and is more resistant to enzyme destruction[8]. It is perhaps for the latter reason that histamine seemed to be less effective in blocking lipolysis induced by dibutyryl CAMP than in blocking the effects of adrenaline.

The data support the idea that histamine might function as an activator of intracellular phosphodiesterase. To relate this observation to the biological actions of histamine, it is necessary to postulate further that normal function of histamine-sensitive cells requires a constant supply of CAMP. By upsetting the balance between synthesis and degradation, histamine might lower the intracellular concentration of CAMP and thereby produce a characteristic biological effect. While the concentration of histamine required to antagonize adrenaline was high, it must be understood that adipose cells, although quite indiscriminate in their response to drugs and hormones, are nevertheless probably not the normal target cells for histamine. The diesterase in smooth muscle cells or in capillary and venular endothelium may be considerably more sensitive.

The suggestion that histamine might act by lowering intracellular concentrations of CAMP is in harmony with a number of well established observations. Theophylline and related compounds which inhibit phosphodiesterase exert antagonistic effects to the action of histamine on bronchiolar smooth muscle[9]. Capillary dilatation induced by histamine can be reversed by sympathomimetic compounds[9] which increase the production of CAMP in many tissues[1]. Furthermore, beta adrenergic blocking agents, which are thought to block adenyl cyclase[10], increase the sensitivity of mice to the lethal effects of histamine[11].

Further work is obviously required to substantiate or refute the hypothesis that the biological effects of histamine stem from an activation of cyclic nucleotide phosphodiesterase. If substantiated, however, this hypothesis may provide important approaches to the development of antihistaminic drugs and to rational therapy for ailments known to be associated with an increase in histamine release.

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Sodium Dependence of the Rate of Onset of the Ouabain-induced Positive Inotropic Effect on Cardiac Muscle

WORK on squid axon[1] has shown a requirement for external Na for the ouabain-induced Na efflux inhibition, for when Na was replaced by choline chloride the rate of Na efflux inhibition was greatly reduced. It is possible that the positive inotropic effect of ouabain on cardiac muscle is connected with its action on the Na + K activated ATPase involved in the transport of $Na^{2,3}$. It has been shown[4] that the extent of the positive inotropic effect on guinea-pig heart is reduced by lowering the concentration of Na and, in atrial muscle[5], this reduces the rate of onset of the ouabain-induced toxic action. I have therefore