

Does Cyclic AMP Play Any Role in Histamine Release from Rat Mast Cells

In recent years there has been an explosive development in research concerning the regulatory role of cyclic AMP. Each year a number of publications bring direct and indirect information about the alleged functions in various biological systems. Histamine release from mast cells and basophils is one of the functions considered to be controlled by cyclic AMP. An elevation of cyclic AMP in target cells is generally regarded to inhibit histamine secretion and the process would hereby conform to a bidirectional regulatory system (Berridge: *Adv. Cyclic Nucl. Res.* 6, 1, 1975). However, this opinion can now be questioned, since data have appeared in the literature which oppose this general concept. The steady accumulation of contradictory information in this area has stimulated us to survey

reports dealing with the cyclic AMP content of secretory cells and its regulatory function on histamine release. Considering possible tissue and species differences, we have chosen to analyse only the reports dealing with isolated rat mast cells, since these cells can be obtained as a pure cell population, which is a prerequisite for proper evaluation of the significance of cyclic AMP data. Furthermore, we have focused interest only on investigations where direct measurements of cyclic AMP have been performed.

Table 1 shows the basal levels of cyclic AMP in rat mast cells in various investigations. The values vary by a factor of about 50. This large variation is difficult to explain even when taking into account differences in experimental procedures: incubation media, strains of rats, and methods

Table 1
Cyclic AMP content of isolated rat mast cells

No.	Cyclic AMP content (pmol/10 ⁶ cells) Mean $\pm$ s.e.m. or range	Methods	References
1	0.30 $\pm$ 0.04	protein binding	Norn et al.: <i>Acta Allergol.</i> 32, 183, 1977
2	0.68 $\pm$ 0.2	protein kinase activation	Johnson et al.: <i>J. Immunol.</i> 112, 511, 1974
3	0.8 $\pm$ 0.24	protein binding	Fredholm et al.: <i>Biochem. Pharmacol.</i> 25, 1583, 1976
4	1.33 $\pm$ 0.33	radio-immuno	Gripenberg et al.: <i>Acta Physiol. Scand.</i> 90, 648, 1974
5	4.2	C ¹⁴ adenine	Hayashi et al.: <i>Biochem. Pharmacol.</i> 25, 1907, 1976
6	4.7 (1-10)	protein binding	Kaliner & Austen: <i>J. Immunol.</i> 112, 664, 1974
7	16 (1.4-161)	radio-immuno	Sullivan et al.: <i>J. Immunol.</i> 114, 1473 and 1480, 1975

Table 2

The influence of drugs which cause elevation of cAMP in rat mast cells on histamine release

Drug	Releaser	References
	Inhibition of histamine release	
PGE ₁	anti-rat Fab	Kaliner & Austen (1974)
Aminophylline		
Theophylline	48/80	Sullivan et al. (1975)
Epinephrine		
Epinephrine	48/80	Hayashi et al. (1976)
Theophylline		
Theophylline	antigen	Norn et al. (1977)
No effect on histamine release		
Theophylline	48/80	Fredholm et al. (1976)
IBMX		
Papaverine		
Papaverine	48/80	Johnson et al. (1974)
PGE ₁		
Activation of histamine release		
IBMX	antigen	Norn et al. (1977)

for determination of cyclic AMP. There appears to be a general agreement that PGE₁, epinephrine, isoproterenol, aminophylline, theophylline, papaverine, and isobutylmethylxanthine (IBMX) elevate cyclic AMP in rat mast cells (see references Table 1). However, only some of these agents inhibit histamine release. Among these the action of papaverine is due to an inhibition of energy metabolism in the cells and not to an elevation of cyclic AMP (Fredholm et al. 1976). Table 2 shows that among agents which all enhance cyclic AMP levels in rat mast cells their influence on histamine secretion varies from inhibition to activation, even with the same releaser. In addition, Sullivan et al. (1975) reported that carbamylcholine and diazoxide reduce the level of cyclic AMP in rat mast cells and in their hands these agents activated histamine release induced by compound 48/80. They also noted that extracellular calcium decreased the cyclic AMP level in the cells. In

contrast, we found no detectable amounts of cyclic AMP in rat mast cells after incubation in a calcium-free medium, whereas 2.5 pmol/10⁶ cells were noted under the same conditions, provided calcium was present (Patkar et al.: *Int. Arch. Allergy Appl. Immunol.*, in press, 1977).

It is evident from the reports available that it is far from certain whether cyclic AMP exerts a modulating role on histamine secretion from isolated rat mast cells and further evaluation is needed. Methods and experimental conditions must be standardized before we know conclusively.

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