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This Week's Citation Classic®

Lichtenstein L M & Margolis S. Histamine release in vitro: inhibition by catecholamines and methylxanthines. *Science* 161:902-3, 1968.
[Johns Hopkins University School of Medicine, Baltimore, MD]

This paper demonstrated that isoproterenol and theophylline inhibited antigen-induced histamine release from human basophils. Moreover, the two drugs were synergistic in their inhibition. We suggested that the effect was due to increased levels of cyclic AMP in the basophils. [The *SCI*® indicates that this paper has been cited in over 475 publications.]

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My interest in immunology began in medical school under the tutelage of David Talmadge. After my internship I took a PhD with Abraham Osler, focusing on immediate hypersensitivity. It soon became apparent that the most interesting and important problem was the mechanism by which antigen interaction with basophil or mast cell immunoglobulin E (IgE) antibody is transduced, so that the cell responds with the release of histamine and the other mediators that cause allergic inflammation. The problem seemed straightforward in the 1960s but has turned out to be far more complex than anticipated; the same questions remain the center of my continuing research activity.

S. Margolis suggested the idea for the experiments outlined in the current *Citation Classic* during a "waiting for the elevator" conversation. He introduced me to the work of Earl W. Sutherland and colleagues,[1] who were then establishing the role of cyclic AMP as a key "second messenger" in the signal transduction of a variety of cells; an increase in the level of this nucleotide accompanied cell activation. We therefore decided to study the effects on basophils of drugs which, in other cell types, caused an increase in cyclic AMP, fully expecting that this would facilitate the secretion of histamine. As has usually happened in my research, our expectation was dead wrong. In fact theophylline and isoproterenol were effective inhibitors of histamine release. In retrospect this is not surprising since these drugs were and continue to be the mainstays of the treatment of allergic disorders.

This experimentation led to a cross-country collaboration with Henry R. Bourne, who was able to measure changes in intracellular cyclic AMP levels, a technique that was not yet available in my laboratory. We studied a variety of inflammatory cell types and several years later wrote a review in *Science* that also became a *Citation Classic*.[2] We promulgated the general theory that increased levels of cyclic AMP in inflammatory cells downregulated their function, in contrast to the findings in other cell types. Perhaps this work and the review were so extensively cited because they extended elegant basic biochemical observations to the field of inflammation. A modulatory role for cyclic AMP in secretory processes was, at that time, central to the thoughts of investigators in many disciplines: cyclic AMP was the "bandwagon" of the late 1960s and the 1970s.

Sometime after writing that review, with the increasing sophistication of experimental design and technique, this simplistic view of the role of cyclic AMP in cell activation was found to be wanting, and the possible importance of this second messenger became increasingly complex. While we would later show that the drugs we used did increase the cyclic AMP levels in purified basophils, simplified theories were rejected, and the exact role of cyclic AMP is still not fully elucidated. In certain rodent mast cells and basophils there is an increase in cyclic AMP after antigen-IgE interaction, although it is not now felt that this represents a central mechanism of signal transduction. In human basophils and mast cells this increase does not seem to occur, but even this remains controversial.[3-5]

This experience taught us that the facile generalizations made early in the exploration of mechanisms of signal transduction are usually false. Thus, the current theories regarding the generation of inositol 1,4,5 triphosphate and diacylglycerol and their involvement in the mechanism of signal transduction have started to become unraveled in the few short years since the discovery of these pathways. Perhaps the bottom line is that the control of cell stimulation or secretion is far more complex than appreciated even at the present time and that visualizing this as a linear process is unlikely to be correct. There almost surely will be multiple second messengers and enzyme systems that feed backward and forward to modulate the process of signal transduction.

1. **Sutherland E W & Robison G A.** Metabolic effects of catecholamines. A. The role of cyclic-3′,5′-AMP in response to catecholamines and other hormones. *Pharmacol. Rev.* 18:145-61, 1966. (Cited 800 times.)
2. **Bourne H R, Lichtenstein L M, Melmon K L, Henney C S, Weinstein Y & Shearer G M.** Modulation of inflammation and immunity by cyclic AMP. *Science* 184:19-28, 1974. (Cited 865 times.) [See also: **Bourne H R.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986. p. 137.]
3. **Ishizaka T, Conrad D H, Schulman E S, Sterk A R & Ishizaka K.** Biochemical analysis of initial triggering events of IgE-mediated histamine release from human lung mast cells. *J. Immunology* 130:2357-62, 1983. (Cited 35 times.)
4. **MacGlashan D W, Schleimer R P, Peters S P, Schulman E S, Adams G K, Kagey-Sobotka A, Newball H H & Lichtenstein L M.** Comparative studies of human basophils and mast cells. *Fed. Proc.* 42:2504-9, 1983. (Cited 55 times.)
5. **Peachell P T, MacGlashan D W, Lichtenstein L M & Schleimer R P.** Regulation of human basophil and lung mast cell function by cAMP. *J. Immunology* (In press.)

IA 16