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Hadden J W, Hadden E M, Haddox M K & Goldberg N D. Guanosine 3':5' -cyclic monophosphate: a possible intracellular mediator of mitogenic influences in lymphocytes. *Proc. Nat. Acad. Sci. US* **69**:3024-7, 1972.
[Depts. Pathology and Pharmacology, Univ. Minnesota, Minneapolis, MN]

The observations implicate cyclic CMP as a positive effector of the proliferative process by virtue of the early increases found to be induced in lymphocytes by the lectin mitogens phytohemagglutinin (PHA) and concanavalin (Con A) [The *SCI*® indicates that this paper has been cited in over 520 publications since 1972.]

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"A series of observations led us to query what the mechanism of lectin mitogen action in lymphocytes might be. The work of others had indicated that lectins might act like hormones. My wife and I were working with Robert A. Good, in the department of pediatrics at the University of Minnesota Medical School, investigating hormone action on lymphocytes. Having probed aspects of the antiproliferative action of cyclic AMP in lymphocytes, we were primed to learn of new mechanisms. I read with excitement of cyclic GMP in the work of Bill George and Nelson Goldberg of the department of pharmacology also at the University of Minnesota.[1] Since others had suggested that the lowering of cyclic AMP was involved with triggering nonlymphocytes to divide, it seemed logical to determine whether mitogen action might involve cyclic GMP in lymphocytes. I approached Nelson with the idea and he, too, thought it a good one.

"We set the experiments up and waited our turn for the cyclic GMP assay, for in those days Nelson and Mari Haddox were involved in measuring cyclic GMP by a time-consuming enzymic cycling assay. With excitement, Nelson presented me the initial results. We promptly completed a series of experiments. The results indicated that three different mitogen preparations induced early increases in cyclic GMP in lymphocytes. We suggested a working hypothesis that cyclic GMP represented at least one of the active signals to initiate cell proliferation and, based on our preliminary experiments with isolated nuclei, that its role might be as a 'membrane to nuclear signal,' a term coined by Good.

"I wrote the paper early one Sunday morning in the attic, interrupted only by Nelson's calls inquiring as to when I would finish. One of its reviewers for the *Proceedings of the National Academy of Sciences* was the late Nobel Laureate Earl Sutherland whose only comment was: 'These observations could be of great potential importance and besides Nelson Goldberg hasn't screwed up yet.' Once published, the paper yielded considerable excitement and controversy as it was the first to link cyclic GMP to cell proliferation. Our experiments with Nelson were extended with Carlos Lopez to show that cyclic GMP increased in serum and insulin-stimulated 3T3 cells in association with the induction of cell division.

"In the decade since, our work in this area has linked the action of lectins to calcium, as well as cyclic GMP, and a series of observations link both to a number of nuclear events including RNA synthesis, RNA polymerases I and II, and nuclear protein phosphorylation. Ron Coffey and I have probed the roles of calcium, phospholipid turnover, and lipoxygenase products in the activation of guanylate cyclase (for a review see reference 2). At least 21 other laboratories have confirmed and extended the original observations to other mitogens and related cyclic GMP increases to activation of cyclic GMP-dependent protein kinase. While many questions remain as to the mechanisms involved, the hypothesis to us still seems valid. Disturbing throughout this decade have been the several reports of failure to confirm. While a number of these may be explained by technical shortcomings in processing extracts and measuring the femtomole quantities of cyclic GMP involved, recent observations of Nelson indicate that the tightly linked (cyclase/phosphodiesterase) metabolic flux of cyclic GMP may be related to signal generation.'This would help clarify how with mitogen stimulation of guanylate cyclase cyclic GMP steady state levels could undergo variable changes depending on the particular system."

1. **George W J, Polson J B, O'Toole A G & Goldberg N D.** Elevation of guanosine 3' ,5' -cyclic phosphate in rat heart after perfusion with acetylcholine. *Proc. Nat. Acad. Sci. US* **66**:398-403. 1970. (Cited 475 times.)
2. **Hadden J W & Coffey R G.** Cyclic nucleotides in mitogen-induced lymphocyte proliferation. *Immunol. Today* **3** 299-304, 1982.