

# This Week's Citation Classic®

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**Berridge M J.** The interaction of cyclic nucleotides and calcium in the control of cellular activity. *Advan. Cyclic Nucl. Res.* 6:1-98, 1975.  
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The action of calcium as a key regulator of numerous cellular processes, including metabolism, secretion, contraction, and cell growth, is modulated by cyclic AMP. Cyclic AMP acts either to enhance (monodirectional control) or to oppose (bidirectional control) the action of calcium. [The *SCi*® indicates that this paper has been cited in over 685 publications, making it the most-cited paper from this journal.]

## The Second Messenger Story

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My interest in second messenger interactions was sparked by a fascinating review<sup>1</sup> written by Howard Rasmussen in 1970, which stressed that cyclic AMP and calcium cooperated with each other as part of a cell communication network. This idea, that cells might be regulated by more than one second messenger, struck a strong chord because at that time my experimental work with William T. Prince on stimulus-secretion coupling in the blowfly salivary gland was beginning to show that cyclic AMP could not explain all the actions of the secretagogue 5-hydroxytryptamine.<sup>2</sup> It just so happened that Rasmussen came to Cambridge for a sabbatical in 1971, and we were fortunate to be able to work with him to prove that calcium was also a key second messenger in stimulus-secretion coupling.<sup>3</sup> At this time, most emphasis at meetings on cell regulation was centered on the cyclic nucleotides, and my attempts to stress the importance of calcium as a messenger fell on deaf ears or was treated with polite indifference. As the voices of the calcium freaks began to prevail, however, it became obvious that these two messenger systems should not be considered as two opposing candidates of cellular control but as two

interacting pathways of a highly coordinated messenger network as originally proposed.<sup>1</sup> I felt very honoured when Al Robison invited me to pull together this information concerning the coordinate activity of these two major messenger pathways into a review for *Advances in Cyclic Nucleotide Research*.

Of the many reviews I have written, this one took the most time because I had to collate information from two separate fields. The task was made all the more difficult because, like many other insect physiologists, I had hitherto paid scant attention to what was happening in other organisms. Most of the reading for this review was done in the magnificent library at Woods Hole during a delightful summer spent in the good company of Betty Wall and Jim Oschman. Between swims in the ocean with the family, I gradually came to grips with the literature on second messengers in vertebrate cells. As I read about how various cell types were controlled, a distinct pattern began to emerge. The interactions between calcium and cyclic AMP, which were a recurring theme, seemed to fall into two categories. In most cells the primary mediator appeared to be calcium, whereas cyclic AMP seemed to be playing a modulatory role, which was to adjust this calcium signal either positively or negatively. In monodirectional systems cyclic AMP acted to facilitate the signal, whereas in bidirectional systems cyclic AMP had an inhibitory effect by opposing calcium. The latter was a particularly interesting system because the antagonistic action of external signals, such as the  $\alpha$ - and  $\beta$ -stimulants of smooth muscle, was reflected in an antagonism of their respective second messenger pathways.

The reason this review has been highly cited is because it brought together information on two second messenger pathways and established the principle that messengers are not separate entities but that they interact at many different levels. I indulged my penchant for drawing diagrams by including 16 figures showing how calcium and cyclic AMP acted in different cell types and suspect that some of the popularity of this review may have been augmented by these visual aids. The ideas for this review were largely moulded by my work on the insect salivary gland, which featured significantly a decade later in the discovery of inositol triphosphate, the subject of an earlier *Citation Classic*.<sup>4</sup>

1. Rasmussen H. Cell communication, calcium ion, and cyclic adenosine monophosphate. *Science* 170:404-12, 1970. (Cited 1,110 times.)
2. Berridge M J & Prince W T. The electrical response of isolated salivary glands during stimulation with 5-hydroxytryptamine and cyclic AMP. *Phil. Trans. Roy. Soc. London B* 262:111-20, 1971. (Cited 25 times.)
3. Prince W T, Berridge M J & Rasmussen H. Role of calcium and adenosine-3',5'-cyclic monophosphate in controlling fly salivary gland secretion. *Proc. Nat. Acad. Sci. USA* 69:553-7, 1972. (Cited 130 times.)
4. Berridge M J & Irvine R. Inositol triphosphate, a novel second messenger in cellular signal transduction. *Nature* 312:315-21, 1984. (Cited 2,460 times.) [See also: Berridge M J. *Citation Classic. Current Contents/Life Sciences* 31(31):16, 1 August 1988; and *CC/Clinical Medicine* 16(31):16, 1 August 1988.]

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