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This Week's Citation Classic

Kuo J F & Greengard P. Cyclic nucleotide-dependent protein kinases, IV. Widespread occurrence of adenosine 3',5'-monophosphate-dependent protein kinase in various tissues and phyla of the animal kingdom. *Proc. Nat. Acad. Sci. US* **64**:1349-55, 1969. [Dept. Pharmacology, Yale Univ. Sch. Med., New Haven, CT]

Cyclic AMP-dependent protein kinase was found in every one of about 30 sources examined, which included many mammalian tissues as well as species representative of eight invertebrate phyla. The data support a unifying theory for the mechanism of action of cyclic AMP, namely, that its many and diverse effects are mediated through activation of cyclic AMP-dependent protein kinase, with the resultant phosphorylation of various cellular proteins. [The *SCI*® indicates that this paper has been cited in over 750 publications since 1969.]

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"Although a great diversity of actions that involve cyclic AMP in many tissues and cells had already been documented,[1] the molecular mechanism for the actions of this intracellular second messenger for hormones remained unknown. The paper by Walsh, Perkins, and Krebs[2] published in 1968 describing a skeletal muscle protein kinase stimulated by cyclic AMP provided the first clue as to how cyclic AMP worked. At that time, Paul Greengard, after spending some time at Vanderbilt University, had just moved from Geigy to Yale University as professor of pharmacology. I, assuming the similar 'industrial shunt,' left Lederle to join him as assistant professor in the department of pharmacology. We teamed up because of our common interest in the cyclic nucleotide systems; thus began our four-year association which was extremely important to the earlier stage of my career. We had evidence showing the occurrence of cyclic AMP-dependent protein kinase in several tissues, including the brain. Greengard suggested (in retrospect, I am glad he did) that we ought to systematically survey the enzyme in mammalian tissues as well as tissues from various invertebrate phyla in order to test its widespread occurrence in the animal kingdom. We found that the enzyme was readily detectable even in the crude extracts of many tissues, but that its presence in many other tissues can be unequivocally established only after the crude extracts were further treated with isoelectric precipitation, ammonium sulfate fractionation, and/or DEAE-cellulose chromatography. Without exception, we found the enzyme in every one of the diverse tissues examined. Based upon the apparently ubiquitous occurrence of cyclic AMP-dependent protein kinase activity, we proposed a unifying hypothesis that the actions of cyclic AMP are mediated through activation of this enzyme. This paper was published in 1969 in the *Proceedings of the National Academy of Sciences of the USA*, most fortunately and appropriately communicated by the late Nobelist Earl W. Sutherland, who, in 1957 with Theodore W. Rall, discovered cyclic AMP.[3] This hypothesis has been tested over the years; it is still considered correct today in all eukaryotic systems.

"In 1970, Greengard and I discovered cyclic GMP-dependent protein kinase, and we further suggested that this enzyme may serve as a mediator for cyclic GMP actions.[4] One obvious determinant for the tissue-specific effects of cyclic AMP and cyclic GMP resides in the nature of tissue-specific substrates that the two cyclic nucleotidedependent protein kinases phosphorylate. This point of view has been dealt with in Greengard's review article[5] entitled 'Phosphorylated proteins as physiological effectors.'

"The reason for the frequent citation of our 1969 paper probably is the particularly attractive feature of the unifying hypothesis which provides a single reaction mechanism by which cyclic AMP can bring about its diverse effects."

1. **Sutherland E W & Robison G A.** The role of cyclic 3', 5' -AMP in responses to catecholamines and other hormones. *Pharmacol Rev* **18**:145-61, 1966.
2. **Walsh D A, Perkins J P & Krebs E G .** An adenosine 3',5' -monophosphate-dependent protein kinase from rabbit skeletal muscle. *J. Biol. Chem.* **243**:3763-5, 1968. [Citation Classic. *Current Contents/Life Sciences* **25**(25): 16, 21 June 1982.]
3. **Rail T W, Sutherland E W & Berthet J.** The relationship of epinephrine and glucagon to liver phosphorylase. IV. Fffects of epinephrine and glucagon on the activation of phosphorylase in liver homogenates. *J. Biol. Chem.* **224**:463-75, 1957.
4. **Kuo J F & Greengard P.** Cyclic nucleotide-dependent protein kinases VI. Isolation and partial purification of a protein kinase specific for guanosine 3', 5' -monophosphate *J. Biol. Chem.* **245**:2493-8, 1970.
5. **Greengard P.** Phyosphorylated Proteins as physiological effectors, *Science* **199**:146-52, 1978.