

Larner J & Villar-Palasi C. Glycogen synthase and its control.

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The paper reviewed the glycogen synthase literature and presented initial evidence for the control of its phosphorylation state and biological activity by cyclic AMP (cAMP) and a protein kinase later renamed cAMP-dependent protein kinase. [The *SCJ*® indicates that this paper has been cited in over 170 publications.]

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This review was written by Carlos Villar-Palasi and me shortly after our move from the University of Minnesota to the University of Virginia. It reviewed the literature of a very exciting, newly discovered enzymatic phosphorylation control system, namely, glycogen synthase. This new system functioning together with phosphorylase, also controlled by phosphorylation but in an opposite direction functionally, produced an integrated system. It also presented a novel nomenclature system for protein kinase and phosphatase cascade systems. In addition, it presented our initial evidence that cyclic AMP (cAMP) activated a protein kinase termed synthase I kinase that was later renamed cAMP-dependent protein kinase.

Studies describing the two forms of the cAMP-dependent protein kinase are detailed, and it is interesting to relate these studies to the two forms that are now known, the inactive holoenzyme and the active catalytic subunit. For example, it was shown that high KCl concentrations selectively inhibited the cAMP-dependent inactive form of the enzyme in contrast to the active or independent form that was only weakly inhibited. In the discus-

sion of the phosphoprotein phosphatase that activated glycogen synthase, the most important fact pointed out was its end-product inhibition by glycogen, key to understanding the inverse relationship found in tissues between glycogen content and independent form (%I), or active form, of glycogen synthase. If this inverse relationship is ignored in this context, it is easy to fall into the trap of concluding that insulin has not had the effect of activating glycogen synthase, a result now recognized as an essentially universal intracellular marker of the hormone action in sensitive cells.

Elucidation of hormonal control by insulin, and later by epinephrine, led to the discovery of the covalent phosphorylation control of glycogen synthase. This was the first example of an enzyme *inactivated* by covalent phosphorylation. About a year later, Tracy C. Linn, Flora H. Pettit, and Lester J. Reed reported pyruvate dehydrogenase to be controlled in a similar manner.<sup>1</sup> Glycogen synthase subsequently became the first example of multiple phosphorylation of an enzyme by several protein kinases within a single chain.

Further studies of the system led to the discovery of insulin mediators. However, the statement in the review that has given me the most pleasure over the years is, "Therefore we would propose that the independent form may be the physiologically active form within the cells." This has turned out to be correct and is almost universally accepted.

This review was interesting to write because it was a very exciting time in the development of the subject and because it contained a number of new ideas and novel concepts and opened a new field of enzymology and hormonal control mechanisms in terms of reciprocal control of the rate-limiting enzymes of glycogen synthesis and degradation. Glycogen synthase and its hormonal and nonhormonal control have turned out to be a gold mine of new information and ideas and a true source of joy for our laboratory and others in many parts of the world.

[See reference 2 for a recent paper in this field.]

1. Linn T C, Pettit F H & Reed L J.  $\alpha$ -Keto acid dehydrogenase complexes. X. Regulation of the activity of the pyruvate dehydrogenase complex from beef kidney mitochondria by phosphorylation and dephosphorylation. *Proc. Nat. Acad. Sci. USA* 62:234-41, 1969. (Cited 300 times.)
2. Larner J, Cheng K, Schwartz C, Kikuchi K, Tamura S, Creacy S, Dubler R, Galasko G, Pullin C & Katz M. Insulin mediators and their control of metabolism through protein phosphorylation. *Recent Prog. Hormone Res.* 38:511-56, 1982.