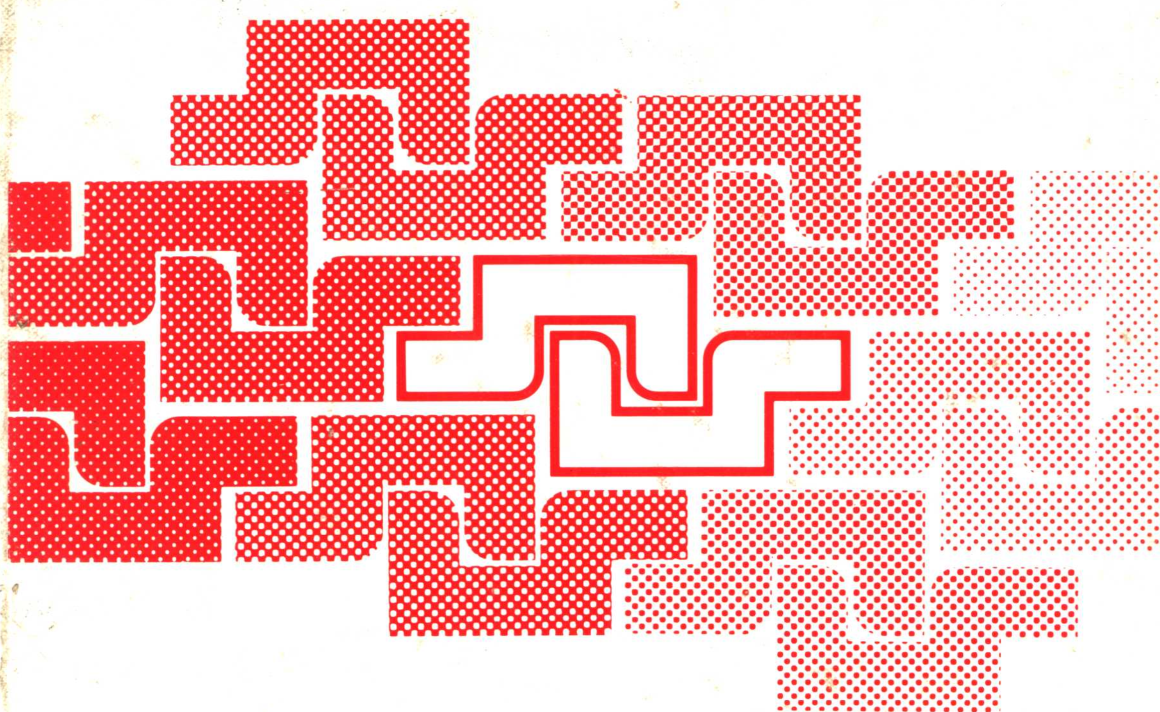

Signal Transduction and Protein Phosphorylation

Edited by

L. M. G. Heilmeyer

NATO ASI Series

Signal Transduction and Protein Phosphorylation

Edited by

L. M. G. Heilmeyer

Institute for Physiological Chemistry I
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PREFACE

A NATO Advanced Study Institute on "Signal Transduction and Protein Phosphorylation" was held to overview recent developments in this area. The participants in the Institute dealt with protein phosphorylation as the most prevalent mode of regulation of cellular processes.

First, methods needed to analyze the complex cascade systems involved were reviewed, including protein sequencing, crystallography, characterization and isolation of membrane proteins, use of monoclonal or polyclonal antibodies and application of fluorescent probes. In great detail the x ray crystallographic structure of glycogen phosphorylase was presented. This enzyme is located at the end of a signal cascade triggered by the hormonal activation of the membrane-bound adenylate cyclase. The interaction of the hormone/receptor with the catalytic subunit of the adenylate cyclase involves GTP-binding proteins. The function of these recently detected intermembrane coupling factors were reviewed, as well as the structure and properties of various protein kinases.

Major emphasis was placed on Ca^{2+} as a second messenger, its metabolism, mechanism of release and uptake from intracellular stores and its role on cell motility and muscle contraction.

Two classes of protein phosphatases were discussed. They differ in their subunit structure and substrate specificity and are subject of a highly complex regulatory mechanism as yet not fully understood.

The general principles of regulation by signal transduction and protein phosphorylation/dephosphorylation were presented in the context of specific cellular processes. These included control of protein synthesis at the translational level and the mechanism of action of interferon. The discussion included the role of protein tyrosine kinases which are structurally related to some oncogene products and, therefore, implicated in various aspects of cell development and transformation.

This text presents the content of the major lectures and important posters displayed and discussed during the Institut's program. It is the hope that inclusion of recent results discussed in the poster sessions presents the reader an impression on the forefront of research in this area. Initiating this book the editor hopes to convey the proceedings of the NATO Advanced Study Institute on "Signal Transduction and Protein Phosphorylation" to a larger audience and to offer a comprehensive account of those developments in an area which is growing very fast.

Ludwig Heilmeyer

Bochum, February 1987

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I. REGULATORY PROPERTIES OF SIGNAL CASCADES

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PROTEIN PHOSPHORYLATION: A HISTORICAL OVERVIEW

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This first lecture will offer a rapid overview of one of the most prevalent mechanisms organisms have devised to regulate their cellular function, that is, phosphorylation-dephosphorylation of proteins.

Prior to 1950, a few phosphoproteins were known. Their main function was thought to be almost exclusively related to food sources for the embryo or the young. This was the case for instance for phosvitin of the egg yolk, casein from the milk, etc. But there was no suggestion that protein phosphorylation could be part of a regulatory mechanism. In fact, at that time, very little was known as to how metabolic processes could be regulated, except that one knew that cellular events could not be controlled solely by adjusting the rate at which proteins or enzymes were synthesized. Cells had to have ways of modulating the activity of their enzymes once these had been produced. They had to have the capability of controlling their economy, rapidly and at all time, in response to changing internal or external conditions, to adapt to their environment or satisfy their metabolic needs.

To describe the origin of the covalent control of enzymes by phosphorylation-dephosphorylation, one must retrace the early history of glycogen phosphorylase with which it is intimately linked. When first discovered in the mid-30's by Parnas in Poland and Carl and Gertie Cori in this country, this enzyme was known to have an absolute requirement for AMP for activity. In 1939, Kiessling in Germany reported that he had obtained a form of the enzyme that was active even in the absence of AMP. The Cori's were so incredulous that the report was largely discounted until three years later when Arden Green in the Cori's own laboratories crystallized phosphorylase in a form that, indeed, did not require AMP for activity. They called this active form phosphorylase _a_, and assumed that it must be the native enzyme since, in the crude extract, it was rapidly converted to the earlier type, that required AMP, which they called phosphorylase _b_. They made the very logical assumption that in native phosphorylase _a_, AMP was covalently bound to the protein as a prosthetic group. Conversion of _a_ to _b_ would then be brought about by a "prosthetic group-removing enzyme". But this is when all the

trouble started: if this hypothesis were correct, AMP would have to be released during the reaction. They found none. In fact, using the most sensitive analytical procedure available at that time, they could detect no AMP, adenine or ribose, either attached to the native enzyme or liberated during the reaction. The Cori's knew that the enzyme existed in two forms, but did not know how these two forms differed and they actually dropped the problem for the next ten years.

Clarification of what really took place occurred ten years later when, with Ed Krebs, we attempted to introduce new procedures for the purification of the enzyme. The classical Cori procedure called for an early filtration of the muscle extract through a battery of filter papers. The operation was cumbersome: as soon as a filter paper became clogged up, one would switch the gunky mess to the next, and so on. So that step was replaced by a centrifugation. But, no matter how carefully or how fast we worked, the preparations always failed: we could never obtain the so-called native, active phosphorylase a, only the degraded b form. Until one day, in desperation, we decided to repeat the Cori preparation to the letter, paper filtration and all, checking every step, analyzing every fraction from beginning to end. And to our amazement, we found out that the very first extract actually contained the inactive enzyme - not the active form. Yet, when the same extract was passed through filter paper, the solution that emerged was active. A conversion of phosphorylase b to a had taken place.

Filtration through paper as a means of activating the enzyme was really unexpected. Actually, it was not as bizarre as originally thought: it so happened that, at that time, all filter papers were contaminated by calcium ions. These were picked up by the extract while passing through the paper, and it was really the calcium ions that did the trick. If the filters were pre-washed with acid or EDTA, no conversion occurred; if calcium ions were then added directly to the extract, activation resulted. It was rapidly found that calcium did not work alone: ATP always present in fresh muscle extract was also required. If the extracts were aged for a while and ATP was hydrolyzed, no conversion occurred until ATP was readded. It then became clear that ATP was involved in a phosphorylation reaction; this was confirmed by the use of radioactive ATP. The original form is totally inactive in the absence of AMP, the phosphorylated species is fully active whether AMP is present or not. Phosphorylation causes a change in conformation of the protein such that the active site which is masked in the b form becomes catalytically operative. The reaction was obviously enzymatic: it had to be catalyzed by a phosphorylase kinase while the reverse reaction had to involve the removal of the phosphate group by a specific phosphatase. Through the action of these two enzymes, phosphorylase could be shuttled back and forth between these two forms in response to cellular demands.

Calcium was essential for the reaction and yet, when the system was finally purified, it was clear that calcium did not participate directly in the b to a conversion, only Mg^{++} and ATP. This meant that calcium had to act at an earlier step, i.e., the activation of phosphorylase kinase, implying that this enzyme itself also existed in an inactive and active state and that calcium was absolutely required for the activation process. This indicated that a sort of cascade of two or three successive reactions was taking place: activation of phosphorylase kinase by calcium ions; the active kinase then activating phosphorylase, which would finally initiate the degradation of glycogen.

It was not known at that time whether this was a rare event restricted to the control of carbohydrate metabolism, or a more widespread type of regulatory mechanism that would apply to other cellular processes. One thing, however, was already clear: the physiologists had known for many years that muscle contraction is triggered when calcium ions are released in muscle cells in response to a nerve impulse. To maintain contraction, one needs energy in the form of ATP. The finding that both processes, muscle contraction and glycogen degradation were triggered simultaneously by calcium ions, explained how these two physiological events could be regulated in concert.

The next observation was that when Ca^{2+}-activated phosphorylase kinase was preincubated with ATP, its activity increased many-fold. The reaction was slow but greatly accelerated by the addition of cAMP. Most probably, it involved a phosphorylation of phosphorylase kinase. Did cAMP simply increase the rate of an autophosphorylation or did it act through a second kinase (it was called "kinase kinase" at first) that might be present as a contaminant? It was only when this enzyme was purified by Ed Krebs and Don Walsh that its nature as a cAMP-dependent protein kinase of broad specificity could be firmly established. At that time, Sutherland had demonstrated that cAMP is produced as a second messenger to turn on a number of metabolic processes (including the activation of phosphorylase) following the binding of a circulating hormone such as adrenaline to a specific receptor in the cell membrane. Today, we know that the hormonal control of glycogen degradation follows this well-known cascade of successive reactions.

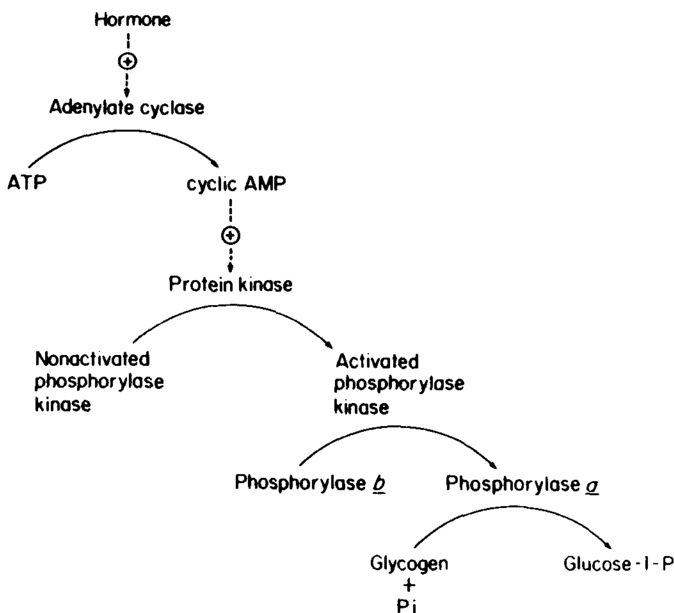

Figure 1.

Everyone of these enzymes is subjected to both allosteric and covalent modification and one might wonder why an organism found it necessary to utilize these two types of regulation? Or again, why have two systems of control evolved simply to convert the inactive form of an enzyme into its active conformation? The

need for allosteric control is obvious: it will primarily reflect intracellular conditions or respond to intracellular needs. For instance, when a muscle contracts, ATP is consumed and glycogen or glucose must be metabolized to resynthesize the ATP needed to maintain contraction. Therefore, many glycolytic or Krebs cycle enzymes would be expected to be activated by AMP/ADP and inhibited by ATP. However, if one had to rely solely on allosteric activation, one would affect simultaneously all the enzymes susceptible to these effectors unless strict intracellular compartmentation existed. In contrast, covalent control is mediated by regulatory enzymes which are generally highly specific. It provides the possibility of affecting a single step without necessarily having to touch any other. Furthermore, covalent modification "freezes" an enzyme in a given conformation, often rendering it insensitive to modulation by the usual allosteric effectors.

In contrast, covalent control by phosphorylation-dephosphorylation will respond primarily to external signals.

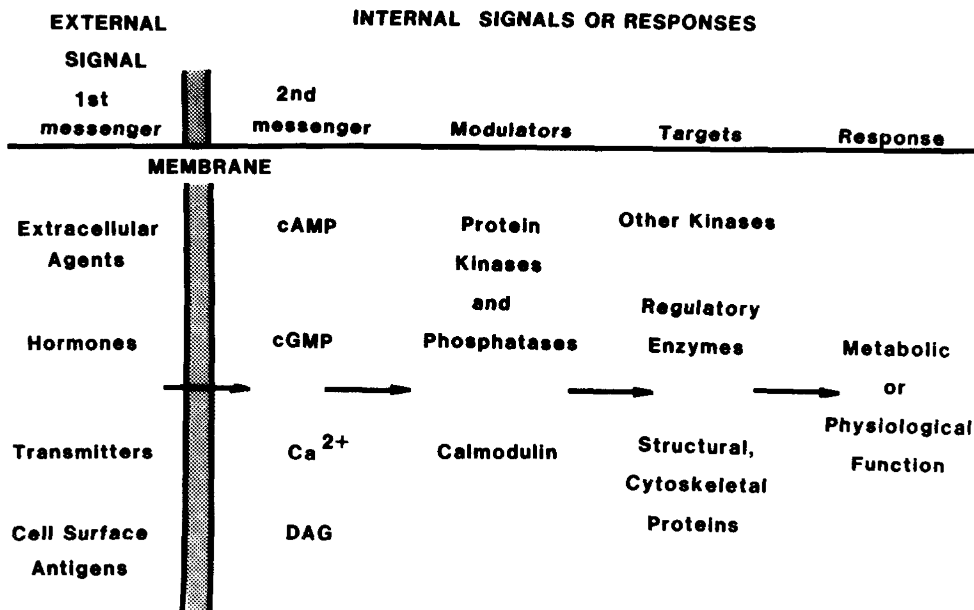

Figure 2.

Consider for example, the control of carbohydrate metabolism in the liver. The prime purpose for regulating glycogenolysis in the liver is to maintain blood glucose levels for the benefit of other organs such as the brain or the erythrocytes, particularly during fasting. Therefore, the sensory mechanism will be external, and the signals sent to the liver to maintain glucose homeostasis will come from the outside -- principally in the form of hormones released from the

adrenals and the pancreas. These external signals will act on the plasma membrane, and their effects will be transmitted inside the cell by various second messengers, such as cyclic nucleotides, calcium, diacylglycerol or other compounds yet to be recognized. Each of these will interact with specific modulator proteins which, in turn, might phosphorylate another enzyme, and ultimately elicit some kind of metabolic or physiological response. One already sees here the elements of a cascade system of control.

What other advantages might such cascade reactions hold? The most obvious is that by having an enzyme acting on an enzyme acting on yet another enzyme, one will have a considerable amplification of an original signal -- something on the order of a million-fold or more. This is why extremely minute amounts of a hormone, or any other compound serving as a metabolic signal, can bring about the mobilization of large quantities of a reserve polysaccharide such as glycogen within a very short time. Stadtman and Chock at NIH have considered this problem from a quantitative point of view and made a theoretical analysis of simulated mono- or polycyclic cascade models. They showed that the process was extraordinarily sensitive to even small variations in the concentrations of the various effectors to such an extend that a ten-billion-fold amplification could be theoretically achieved in a four-cycle cascade process in which each parameter varies only by a factor of two.

Equally important, if not more so, is that cascade reactions have pleiotropic functions.

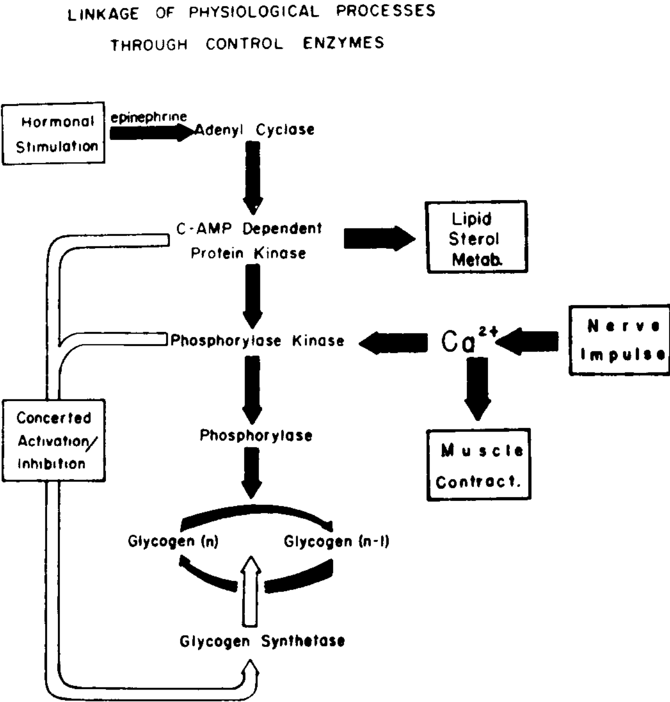

Figure 3.

That is, each of the regulatory enzymes involved can affect a number of proteins from other metabolic pathways, in effect linking different physiological processes to one another. As already mentioned, adenylate cyclase serves as the link between the endocrine system and many intracellular pathways, including those of carbohydrate metabolism. Phosphorylase kinase links the same process to muscle contraction: following neural stimulation, calcium released from the sarcoplasmic reticulum will trigger contraction by binding to the troponin complex on the thin filament, or to myosin light chain kinase through its modulator protein, calmodulin. By the same token, it will trigger glycogen breakdown by activating phosphorylase kinase. The third member of this cascade, the cAMP-dependent protein kinase, plays a pleiotropic role par excellence, since it can link carbohydrate metabolism to a number of other pathways such as lipid metabolism (by acting on the hormone-sensitive lipase), cholesterol metabolism (through cholesterol esterase), steroid metabolism (through HMG CoA reductase) and so on. Both cAMP-dependent protein kinase and phosphorylase kinase will also act on glycogen synthase; however, while protein phosphorylation activates phosphorylase, it inhibits glycogen synthase. This affords a synchronous but opposite control of the activity of the two enzymes. It renders the system exquisitely sensitive to slight variations in the concentration of a number of effectors acting in a reciprocal manner. It also prevents the establishment of a futile cycle which would be engendered by the simultaneous synthesis and breakdown of glycogen, thus providing a safeguard against a useless utilization of ATP.

There is perhaps another advantage of relying on the covalent modification of proteins. All such regulatory enzymes have oligomeric structures, and there is no reason why the modification reaction should proceed in an all or none fashion. In the case of phosphorylase, if partially phosphorylated intermediates were produced,it is possible that the properties of the enzyme would be neither those of phosphorylase b nor a. These intermediates which could be active in the presence of substrates (P_i or G1P) would be strongly inhibited by physiological concentration of G6P. Therefore, small variations in the relative proportion of these sugar esters might afford a sensitive and effective means of controlling glycogen utilization.

Finally, it would be quite impossible to pack all the information needed for such multiple interactions within a single protein. Therefore, all the excess of information required for calcium regulation, hormone recognition or interaction with other metabolic pathways can only be stored in annex molecules, just as one would store excess information in a second disc on a computer when the first one has become saturated. In fact, it is for this reason that most of these regulatory enzymes are themselves made up of different subunits, each with the complement of information it needs to carry out its characteristic function.

Cellular regulation by enzyme phosphorylation

When control of enzyme activity by reversible phosphorylation was first uncovered, one didn't know whether this would be a unique occurrence or a more general phenomenon which might apply to a number of other systems. Would protein phosphorylation be restricted to enzymes involved in carbohydrate metabolism? Would enzymes involved in nitrogen metabolism be covalently modified by,

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