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MINI-REVIEW

Transmembrane Signaling, Then and Now: The Decade of the Eighties

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Abstract

The chronology of the major discoveries important in elucidating certain aspects of the molecular basis of transmembrane signaling is briefly reviewed. Recent developments linking cell stimulation and transformation are intimated.

Key Words: hormones; receptors; second messengers; protein kinases.

When asked how a cell responds to signals in its environment, a biochemist or cell biologist will instinctively respond; "an agent binds to a specific receptor on the plasmalemma, which results in the generation of a second messenger that activates a protein kinase. Alternatively, a hormone, for example, may bind to a receptor that possesses tyrosine kinase activity." Additional terms such as "G-proteins," "phospholipid turnover," "arachidonate metabolites," and "protein phosphorylation cascades" are likely to be mentioned.

It is thus hard to imagine that less than 40 years ago most of these terms were largely meaningless. However, the period 1954 through 1958 saw several major discoveries that would illuminate and direct inquiries into this area for years to come. These included the first descriptions of a protein kinase (Burnett and Kennedy, 1954) and a second messenger (Rall and Sutherland,

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1958), along with the recognition that a cellular protein (i.e., glycogen phosphorylase) could undergo enzyme-catalyzed phosphorylation and dephosphorylation with physiological consequences (Sutherland and Wosilait, 1955; Fischer and Krebs, 1955). A particularly insightful, though less understandable, observation made during this period was that pancreas slices from pigeons stimulated cholinergically exhibited a marked incorporation of ^{32}P into phosphatidylinositol and phosphatidate (i.e., the "phospholipid" or "Hokin" Effect; see, e.g., Hokin and Hokin, 1955, 1958). Nearly three decades would pass before a complete biochemical explanation for this phenomenon would emerge.

Many of the discoveries of the 1950's had their origins in concepts which evolved during the previous decade in the laboratory of Gerty and Carl Cori at Washington University in St. Louis. There, research on glycogen metabolism and, in particular, the effects of hormones on the activity of the enzyme phosphorylase in liver slices (Cori and Green, 1943; Cori and Cori, 1945) set the stage for the subsequent discoveries of protein phosphorylation and *c*AMP. It is noteworthy that the seminal studies on nerve growth factor were also performed at Washington University around this same period (Levi-Montalcini and Hamburger, 1951, 1953). Pioneering investigations on the chemical reactions involved in the visual cycle (see, e.g., Wald, 1934) and on the slow reacting substance of anaphylaxis (see, e.g., Feldberg and Kellaway, 1938) also preceded the mid 1950's.

Deeper conceptual insights into the biochemical mechanisms of signal transduction were gained in the 1960's and 70's. Of paramount significance was the formulation of the "two-messenger system" of hormone action by Sutherland (Sutherland *et al.*, 1965). The first messenger is the hormone itself which, upon arrival at the effector cell, promotes the formation of a "second messenger" within the cell that initiates the response. Other particularly noteworthy conceptual developments included the recognition of a role for a guanosine triphosphate binding protein (G-protein) in the regulation of adenylate cyclase (Rodbell *et al.*, 1971) and the demonstration that a second-messenger could activate a protein kinase (Walsh *et al.*, 1968). These observations would subsequently be shown to represent motifs in a variety of signal transduction pathways. This period was also marked by several other noteworthy events. Calmodulin, a Ca^{2+} binding protein that mediates the effects of Ca^{2+} on a wide variety of enzymes, was described in 1970 (Cheung, 1970). The technique of affinity chromatography allowed the first hormone receptor to be purified in 1972 (Cuatrecases, 1972). A causal relationship between the "phospholipid effect" and alterations in cellular Ca^{2+} was hypothesized in 1975 (Michell, 1975). The chemistry and physiology of certain lipid mediators were also illuminated during this time. The prostaglandins, short-lived local hormones, were shown to be derived from

arachidonic acid in the mid 1960's (see, e.g., Bergström, 1967). Another class of arachidonate-derived messengers, the leukotrienes, was characterized during the period of 1979 to 1983 (see, e.g., Borgeat and Samuelsson, 1979). The structure of the slow-reacting substance of anaphylaxis, a leukotriene, was elucidated in 1979 (Murphy *et al.*, 1979), nearly 40 years after its discovery.

Several major discoveries in the 1980's resulted in a clear and exact understanding of the nature of the "phospholipid effect." A specific phospholipase C was found to catalyze the hydrolysis of a minor membrane phospholipid, phosphatidylinositol 4,5-bisphosphate, to produce two second-messenger molecules in a single reaction; *sn*-1,2-diglyceride and inositol (1,4,5)-trisphosphate. The former activated a recently described phospholipid- and Ca^{2+}-activated protein kinase (protein kinase C; see Kishimoto *et al.*, 1980), whereas the latter promoted the release of Ca^{2+} from the intracellular storage sites for this cation (Streb *et al.*, 1983). These messengers were capable of interacting synergistically in a variety of fashions to amplify cellular responses (see, e.g., Kaibuchi *et al.*, 1983; Badwey *et al.*, 1988). Perhaps the single most important discovery that was made during this decade was that certain xenobiotic tumor promoters (e.g., phorbol esters) could substitute for endogenously generated diglyceride in activating protein kinase C (Castagna *et al.*, 1982). Thus, this kinase was shown to be the cellular receptor for phorbol esters and some of the other tumor promoters. This observation immediately forged links between the study of cell stimulation and of transformation, and bridged the areas of signal transduction and regulation of cell growth. Diglycerides are known to be rapidly metabolized by cells, whereas tumor promoters are not. An implication of this is that while a transient activation of protein kinase C is involved in cell stimulation, the chronic activation of this kinase may predispose the cell to transformation. It was soon established that the increases in diglyceride observed in stimulated cells could arise from sources other than the phosphoinositides (see, e.g., Daniel *et al.*, 1986) and that diglyceride was, in fact, elevated in some transformed states (see, e.g., Preiss *et al.*, 1981). G-proteins were purified and extensively characterized during this period (Sternweis *et al.*, 1981; Bokoch *et al.*, 1983). Of importance to the above discussion was the observation that G-proteins modulated certain C- and D-phospholipases (see, e.g., Ohta *et al.*, 1985; Irving and Exton, 1987), and could thus affect the cellular levels of diglyceride.

Protein kinase C catalyzes the phosphorylation of its substrate proteins on serine and threonine residues. Early in the 1980's, it was recognized that the epidermal growth factor receptor (Ushiro and Cohen, 1980) and the insulin receptor (Kasuga *et al.*, 1982) contained intrinsic kinase activity toward certain tyrosine residues of proteins. Unfortunately, the role of

tyrosine phosphorylation in cell stimulation is not well understood. However, strong evidence is accumulating that certain of the substrates of these tyrosine kinase activities are themselves serine/threonine protein kinases, and that these enzymes are activated by phosphorylation on tyrosine residues (see, e.g., Morrison *et al.*, 1989). A growing chain of evidence that links normal elements of signal transduction pathways to growth and transformation is being provided by the frequent discovery of oncogenes that code for proteins possessing tyrosine kinase (e.g., src), serine/threonine kinase (e.g., Raf-1), and GTP-binding (ras) activities (for review, see, e.g., Bishop, 1983).

The series of mini-reviews presented in this volume discusses and amplifies many of the discoveries briefly outlined here. While research performed during the 1980's certainly clarified some of the major questions regarding signal transduction, others were raised. For example, what are the functions of the novel inositol phosphates (see, e.g., Batty *et al.*, 1985) and phospholipids (e.g., phosphatidylinositol 3,4-bisphosphate; see Auger *et al.*, 1989) which have recently been uncovered? What general mechanisms may relate the tyrosine kinase activities of certain receptors to that of the serine/threonine kinases which are known to become functional when these receptors are occupied? If the progress of the 1980's is any indication, the next decade will surely be marked by even greater advances in these areas.

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