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**Michell R H.** Inositol phospholipids and cell surface receptor function.
*Biochim. Biophys. Acta* 415:81-147, 1975.
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By the mid-1970s, it was clear that a rise in cytoplasmic $Ca^{2+}$ concentration is an essential component of many of the responses of cells to hormones, neurotransmitters, and other extracellular stimuli. It then became clear that the same stimuli invariably enhance the turnover of inositol phospholipids. In this review article, I developed the idea, which has since been proved correct, that receptor-triggered inositol lipid hydrolysis is a transmembrane signalling reaction that causes the mobilization of $Ca^{2+}$ within stimulated cells. [The *SCI*® indicates that this paper has been cited in over 1,755 publications.]

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In the early 1960s, when I studied for my PhD with J.N. (Tim) Hawthorne,[1] phospholipids were regarded as the greasy permeability barrier within biological membranes. However, the inositol phospholipids, which constitute only a small fraction of this membrane lipid, behaved in a unique manner; Mabel R. Hokin and Lowell E. Hokin[2] had shown that inositol phospholipids, unlike other membrane lipids, show enhanced metabolic turnover when many cells are stimulated. Hawthorne passed on to me his fascination with this striking and enigmatic observation, so I went to Harvard Medical School to participate in Manfred Karnovsky's investigations of this response in phagocytizing neutrophils.

However, other studies intervened, and stimulated inositol lipid metabolism took a backseat until the early 1970s, when Eduardo Lapetina, David Allan, Lynne Jones, and I attacked it intensively. We realised that this response involved inositol lipid hydrolysis and was implicated in diverse cellular responses to stimuli and also that it was triggered by a mechanism that did not involve the all-conquering cyclic AMP. We then recognised that it always coincided with receptor-activated mobilization of $Ca^{2+}$ within stimulated cells. Once we were sure that receptor-activated inositol lipid hydrolysis was not caused by the mobilized $Ca^{2+}$, there were only two possibilities: either inositol lipid hydrolysis and $Ca^{2+}$ mobilization were unrelated events or inositol lipid hydrolysis caused $Ca^{2+}$ mobilization. We elected the latter as the more parsimonious and experimentally testable working model; and it was written up, sent to *Nature*, and rejected. At that time I fortunately had deferred my response to an invitation to write for *Biochimica et Biophysica Acta's Biomembrane Reviews*. Coincidence of the new ideas with the impending arrival of a baby provoked me to write my review in the summer of 1974, so our idea first appeared in 1975 as the central conclusion of an extensive review article rather than as a brief letter.

In the next few years, general interest in the possibility that inositol lipid breakdown might be a widespread and very important transmembrane signalling reaction was relatively slow to develop, and this idea was forcefully opposed by some workers until about 1983. However, by 1984 it had been shown that phosphatidylinositol 4,5-bisphosphate is the lipid hydrolysed in response to stimulation[3] (another idea that *Nature* didn't want to publish and that first appeared in an invited review) and that the two products of this reaction are second messengers: 1,2-diacylglycerol activates Yasutomi Nishizuka's protein kinase C,[4] and inositol 1,4,5-trisphosphate links receptor activation to the release into the cytosol of $Ca^{2+}$ from an intracellular store.[5] The cellular processes in whose control this system has since been implicated are legion; they include the fertilization of eggs, liberation of stored carbohydrate from the liver, and the switching on of immune cells by antigens. Moreover, it is now clear that other, previously unrecognised inositol lipids have specific cellular functions, including the anchoring of cell surface proteins and possibly the generation of a mediator of insulin action, and that mammalian cells contain substantial quantities of structurally diverse inositol phosphates whose functions are yet to be determined.[6]

As a result of my contributions to the recognition that inositol lipids play a central role in cellular signalling processes, I have been elected to the Royal Society and now hold a Royal Society Research Professorship, and I have been awarded the CIBA Medal of the Biochemical Society.

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2. **Hokin M R & Hokin L E.** Enzyme secretion and the incorporation of $P^{32}$ into phospholipids of pancreas slices. *J. Biol. Chem.* 203:967-77, 1953. (Cited 315 times since 1955.)
3. **Michell R H, Kirk C J, Jones L M, Downes C P & Creba J A.** The stimulation of inositol lipid metabolism that accompanies calcium mobilization in stimulated cells: defined characteristics and unanswered questions. *Phil. Trans. Roy. Soc. London B* 296:123-37, 1981. (Cited 325 times.)
4. **Nishizuka Y.** The role of protein kinase C in cell surface signal transduction and tumour promotion. *Nature* 308:693-7, 1984. (Cited 2,070 times.)
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6. **Berridge M J & Michell R H, eds.** *Inositol lipids and transmembrane signalling.* London: Royal Society, 1988. 436 p.



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