## Ten years of Dahlem Conferences

**THE meeting on the molecular mechanism of photoreception was the fortieth workshop run by the Dahlem Conferences and marked the tenth anniversary of the organization with a flourish.**

**Founded in 1974 by the German Association for the Promotion of Sciences and Humanities in cooperation with the Deutsche Forschungsgemeinschaft, the Dahlem Conferences are financed by the founders, the Senate of the City of Berlin and various commercial interests. They aim to promote the international interdisciplinary exchange of scientific information and ideas, and to stimulate international cooperation in research. Four meetings a year are held in Berlin, usually three on biological topics and one in physical sciences. The areas chosen are usually complex and tend to cut across traditional subject boundaries.**

**The success of the meeting lies in the format of the workshops, which has been developed, under the leadership of the director, Dr. Silke Bernhard, to ensure a high level of discussion. About 40 participants from all over the world are invited to each meeting, with a number of places reserved for German research students. Background papers are circulated before the meeting so that the four small discussion groups within each workshop can concentrate on areas of uncertainty and identify new questions and directions. The discussions of each group are presented as a summary report at a final meeting of all participants, and then revised in the light of this debate. These reports, together with the background papers, are published rapidly as a book in the series 'Dahlem Workshop Reports'.**

**Each Workshop lasts a week and gives plenty of opportunity for informal meetings between participants, outside the working sessions. This has faciliated many international and interdisciplinary collaborations and allows people to discuss points of difference in private. As a mark of its success, the 'Dahlem model' has been adopted as a basic format for many other conferences.**

**The anniversary was celebrated on 12 December 1984 with a seminar for the founders and sponsers, at which six participants of previous Dahlem conferences recounted their impressions of the meetings and described the effects on their subsequent research.**

**Topics for the 1985 workshops are biotechnology, phanerozoic life and mechanisms of cell injury.** Jennifer Altman.

the suggestion that the high energy turnover involved in the flux, rather than absolute concentrations of cyclic GMP, could play the key role in phototransduction (N. Goldberg, University of Minnesota). The alternative, and more likely, view is that the energy stored in the cyclic GMP molecule does not have to be harnessed on hydrolysis but rather ensures that hydrolysis has a high activation threshold and proceeds very rapidly once initiated — both necessary properties for a good switching mechanism. A bucket of water on a high building is a good analogy: stable until pushed off the edge, when it falls rapidly (E. N. Pugh Jr. University of Pennsylvania). In the rod, small local conentrations of cyclic GMP at the channels would be sufficient, and K.-W. Yau (University of Texas, Galveston) gave an estimate of 1 – 15 $\mu$M of free cyclic GMP per rod.

Up to now, however, there has only been speculation about the way that cyclic GMP could control the photosensitive current. The most common model, derived from other cyclic nucleotide messenger systems, involves phosphorylation of channels in the dark to keep them open, using a cyclic GMP-activated kinase, and a phosphatase to dephosphorylate the channels and close them when cyclic GMP levels drop in the light. So far, cyclic GMP-dependent kinases and phosphatases have not been convincingly demonstrated in rods (M.D. Bownds, University of Wisconsin). On theoretical grounds, Pugh argued that a kinase/phosphatase mechanism is unlikely as it would be energetically too costly, because of the speed of the photoresponse (see also ref. 5).

His argument received experimental support at the end of the last discussion session, when Yau electrified the whole meeting by describing experiments by Fesenko *et al.*[2] and his own group (unpublished), where bathing the inside of isolated patches of ROS membrane with cyclic GMP produced a rapid, reversible increase in conductance. The effect is not dependent on ATPase or GTPase and occurs in the absence of kinases and phosphatases. Changes in calcium concentration, in the absence of cyclic GMP, have no effect on conductance at all. This is clear evidence that cyclic GMP acts directly on the channels to keep them open, probably by cooperative, allosteric binding. Similar observations of conductance changes controlled directly by cyclic GMP have also been made for disk membranes *in vitro* (ref. 18; Kaupp).

The idea of channels held open in the dark by cyclic GMP fits well with data on channel kinetics[15]. The light-sensitive ROS channels are far smaller than any other known channel — they pass an average current of $4 \times 10^{-15}$A. In the dark about 10,000 per rod are open at once, with a mean open time of 2 ms. Light reduces the opening rate; that is, once channels close they do not open again, which is consistent with the idea that cyclic GMP is removed by hydrolysis in the light.

Even so, the game is not yet over. Both Matthews *et al.*[4] and Cobbs and Pugh[5] find that exogenous cyclic GMP does not slow the rising phase and prolongs the duration of the photoresponse, both inconsistent with the idea that a simple binding of cyclic GMP keeps channels open. Although the allosteric binding reported by Fesenko *et al.*[2] goes some way to resolving this anomaly, theoretical analysis indicates that the free cyclic GMP would have to be much lower than published estimates and that the bound cyclic GMP must be inexchangeable on the time scale of the rising phase of the photoresponse[5]. Moreover, although it is no longer creditable as the messenger, calcium seems to play some role since $Ca_i$ in the rod is carefully regulated[3] — it could be involved in adaptation of the light response by modulating enzymic activities. More intriguing still is the recent discovery of inositol trisphosphate (ins $P_3$) in vertebrate photoreceptors and the possibility that there are branched pathways in the transduction mechanism (J.E. Brown, Washington University, St. Louis), particularly as Ins $P_3$ seems to be involved in releasing bound calcium in many cells[19]. So although the results of Fesenko *et al.* and Yau are a breakthrough in understanding phototransduction in vertebrate rods, clearly there are still baroque complexities to be unravelled.

Are these features specializations of photoreceptors, or could they have far-reaching implications? This is the first time that a cyclic nucleotide has been shown to regulate any channel directly, rather thanthrough protein phosphorylation; are other examples waiting to be found? Are the tiny light-sensitive channels, carrying currents that are within the noise level of patch clamp recordings, unique to the ROS, or could they be lurking among the larger channels in other excitable membranes? The highly sophisticated techniques needed to work on tiny photoreceptor cells are providing new challenges to those working on ostensibly more straight-forward systems. □


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