state of phosphorylation[2,9].

Another, apparently larger glycopeptide and two smaller peptides (M_rs=30K and 50K) are non-covalently associated with the DHP-binding subunit (see, for example, ref. 8). The glycopeptide is being cloned, and the amino-acid sequence which can be deduced from the cDNA sequence should assist in predicting its arrangement in the molecular assembly. The remarkable resemblance of the DHP-receptor peptide to Na^+-channel peptides suggests that it folds into four membrane-spanning domains arranged in a pseudo-tetramer in the bilayer. How could another subunit of similar size be accommodated? It could form a companion structure, perhaps in a dissimilar conformation. A loosely paired organization would explain the small size of the irradiation inactivation target for the DHP receptor (M_r=210K)[10]. This notion seems a little less *ad hoc* in the light of dramatic new information about the ryanodine receptor with which it may interact.

Ryanodine is a neutral plant alkaloid which causes the dumping of SR Ca^{2+} stores. When heavy SR membranes are fused into planar bilayers, a multi-state cationic channel is observed which is highly conductive to Ca^{2+}, is activated by micromolar Ca^{2+} and by millimolar ATP, and blocked by calmodulin and ruthenium red. This channel is locked into a conducting substate by ryanodine (see ref. 11). Thus the ryanodine receptor, exclusively associated with the terminal cisternae, seems to be the outstanding candidate for the Ca^{2+}-release channel.

Biochemical isolation of the detergent-solubilized ryanodine receptor reveals a very large particle of M_r about 1,800K (refs 12, 13). The protein is apparently formed of four identical peptides of 400K–450K. When reconstituted into artificial bilayers, the full range of conductance and pharmacological properties attributed to the ryanodine receptors in heavy SR can be reproduced.

Remarkably, when this receptor was examined under the electron microscope, investigators found themselves staring at the SR foot[12–14]. Fleischer and co-workers have recently performed a detailed examination of the morphology of the particle[14]. As illustrated in the figure, it displays an elaborate 4-fold symmetry, and is inserted at one end into the cisternal membrane. Extending more than 120 Å into the triadic gap is a large clover-leaf or quatrefoil structure, which seems very likely to associate with the t-tubule via the DHP-receptor complex.

Among the implications of these findings, assignment of the Ca^{2+} release site to the SR feet, the one structure which physically spans the gap, reinvigorates the hypothesis of Chandler and co-workers[15] that direct conformational coupling links the voltage-sensor in the t-tubule to the SR channel[15]. (Reconstituting such a postulated intermembrane coupling could be feasible, perhaps by driving the opening of ryanodine receptors with Ca^{2+} channel agonists in preparations where intermolecular associations are retained). The extended quatrefoil surface which the ryanodine receptor presents to the t-tubule makes the involvement of a 'dimeric' DHP receptor, or a pair of such assemblies, seem more inviting.

Although these discoveries legitimize a discussion of direct allosteric coupling mechanisms, other phenomena must be considered in the overall cycle of events. Demonstration that Ca^{2+} readily activates conductance of the ryanodine receptor has already stimulated a re-examination of the importance of Ca^{2+}-activated Ca^{2+} release, together with the question of how this conductance is terminated to permit Ca^{2+} reuptake[6].

Furthermore, potential roles for the inositol trisphosphate cascade continue to present themselves. In SR membranes from frog skeletal muscle, as well as smooth muscle, inositol 1,4,5-trisphosphate has now been shown to activate ryanodine-sensitive Ca^{2+} conductances[16]. Does this relate directly to coupling or to modulation of the effects of conformational activation by the DHP receptor? Given the importance of maintaining control of Ca^{2+} levels at all stages of the excitation–contraction coupling, could this cascade be involved in maintaining Ca^{2+} homoeostasis, including recruitment of extracellular Ca^{2+} into the intracellular cycle? If this turns out to be true, is there a role for other products of the cascade, and how are the responsible enzymes activated? Needless to say, the fascinating paradoxes surrounding excitation–contraction coupling remain unresolved, but we can assert that our state of confusion has advanced to a new level of sophistication. □

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Daedalus

Counting stars

STELLAR distances are estimated in many ways. The most basic method, which calibrates all the others, is that of orbital parallax: measuring the tiny shift in a star's position as seen from opposite sides of the Earth's yearly orbit round the Sun. Sadly, this method will only work with rather close stars — within a couple of hundred light years or so. Daedalus now has a new method.

At some point in its orbit, he says, the Earth is closest to the target star; six months later it is furthest away. So the star should fluctuate in apparent brightness on a yearly cycle, with a maximum when the Earth is closest, and a minimum when it is most distant. The effect would be very small. But Daedalus points out that the intensity of light can nowadays be measured with absolute precision, by photon counting. This is already used in many telescopes, and could easily be adapted to integrate the light from a single star.

The snag, of course, is that light is inherently 'noisy'. A photon count is reproducible only to within about the square root of the total count. Even so, Daedalus calculates that a telescope of ten square metres cross-section, counting for a fortnight, could measure the brightness of a star like the Sun sufficiently precisely to register its yearly brightness cycle from 500 light years away. Bigger mirrors, longer integration times, and brighter target stars could extend the technique to far greater distances still.

No earthbound instrument, peering through the turbulent soup of the atmosphere, could do this job. A space-borne telescope is essential, but need not be very expensive. A photon-counting detector does not need a sharp stellar image, so a very crude mirror should suffice: just good enough to separate the target star from its neighbours. Daedalus envisages a plastic-film balloon, inflated in the zero-gravity vacuum of space into just the right curvature for its aluminized back face to form a simple concave mirror. It will be roughly attitude-stabilized to keep its imperfect image of the chosen star on the photomultiplier array at the instrument's focus. The count would be relayed continuously to Earth. The whole thing should not tax the state of the art in any direction, and might be an ideal European contribution to space technology.

Daedalus would be particularly pleased to see his new instrument used to measure the distances of quasars. These are now so universally assumed to be immensely bright and immensely distant that the proof of the converse belief would set a corrective cat among a flock of rather self-satisfied pigeons. David Jones