Marriage of the flytrap and the serpent

Bruce R. Conklin and Henry R. Bourne

THE cloning of a sensor for extracellular calcium, described by Edward Brown and colleagues in *Nature* last month¹, reveals the evolutionary marriage of two protein structures that hail from different kingdoms. One works (and looks) like a Venus flytrap and belongs to a family of bacterial detectors for ions and nutrients. The other, a serpentine receptor coupled to G proteins, is found in myriad incarnations in eukaryotes, where it serves as a detector for light, pheromones, odours, hormones and neurotransmitters.

The newly discovered sensor regulates secretion of parathyroid hormone (PTH), the principal hormonal regulator of serum Ca^{2+} in mammals. Acting in bone, kidney and the gut, PTH raises serum Ca^{2+} (see figure). Appropriate regulation of PTH secretion requires that PTH-secreting cells in the parathyroid glands 'sense' ambient serum calcium². The newly cloned sensor responds to increased levels of extracellular Ca^{2+} by triggering a phospholipase-C-dependent pathway that tells the cell to decrease PTH secretion.

Brown and collaborators in the Seidman laboratory have moved fast to highlight the physiological significance of the sensor. In the latest issue of *Cell*³ they report the obvious gene-knockout observation — and in an increasingly popular animal model, people. Inheritance of one inactive calcium sensor gene causes familial hypocalcaemic hypercalcaemia (FHH), a mild heterozygous, dominant disorder characterized by modestly elevated serum Ca^{2+} , normal PTH levels and inappropriately low urine Ca^{2+} . Together, these findings suggest that patients with FHH have a raised 'set point' for extracellular Ca^{2+} (normally, increases in serum Ca^{2+} lead to decreased PTH levels and increased urinary Ca^{2+} excretion). Serum Ca^{2+} is much higher in the unfortunate infant who inherits two defective Ca^{2+} sensor genes; this homozygous, recessive disorder is lethal unless the parathyroid glands are surgically removed.

Identification of a calcium sensor sparks new hopes for finding the sensors of other extracellular ions. Which ion will next achieve the status of a hormone? Some of the candidates (Mg^{2+} , PO_4^{2-} , Na^+ , Cl^-

and H^+) are already known to activate second messenger systems associated with G protein-coupled receptors². Routine clinical measurements of ion concentrations have led to discovery of genetic disorders characterized by abnormal

The calcium sensor's role in parathyroid hormone (PTH) secretion and calcium homeostasis. The extracellular domain is shown closing upon binding to calcium, analogous to the action of a Venus flytrap. PLC, phospholipase C; the G protein is shown as G_q (the subclass of G protein thought to activate PLC).

extracellular concentrations of ions⁴ such as K^+ , PO_4^{2-} and Mg^{2+} . Inherited mutations of an ion receptor could account for either an increase or a decrease in the extracellular concentration of that ion, depending upon whether the mutation inactivates the receptor or makes it more than normally sensitive to its ligand (the second possibility is less likely, but has precedents among G protein-coupled receptors⁵).

The Ca^{2+} sensor is unusual among serpentine receptors because it has an enormous extracellular domain of 605 amino acids at the amino terminus (see figure). This domain probably serves as the actual Ca^{2+} detector, while the serpentine domain (composed of the seven membrane-spanning segments characteristic of G protein-coupled receptors) transmits the message across the membrane. Of the three point mutations in

FHH patients³, two are in the extracellular domain and one in a portion of the serpentine domain predicted to contact G proteins⁶. Similarities in amino-acid sequence suggest that the extracellular domain is a modified version of a large family of periplasmic binding proteins (PBPs) that are involved in bacterial nutrient uptake; these proteins bind ions and other nutrients in the periplasm, and deliver them to transporter proteins that move the nutrients across the plasma membrane⁷. Crystal structures of PBPs resemble a Venus flytrap, with two lobes that move like a pincer to envelop the ligand⁸.

The first described resemblance between PBPs and serpentine receptors involved the metabotropic glutamate receptor, whose extracellular ligand-binding domain has been modelled after the PBP structure⁹. Strikingly, in FHH patients both point mutations in the extracellular domain of the Ca^{2+} sensor align with the predicted ligand contact sites of the metabotropic glutamate receptor (refs 3 and 9; P. J. O'Hara, personal communication). Such mutations support the speculative idea that Ca^{2+} binding triggers the two lobes of the Ca^{2+} sensor's extracellular domain to bend towards one another, producing a large conformational change that in turn tells the serpentine domain to activate G proteins.

The calcium sensor's role in physiology is at long last emerging, and the sensor's identification illustrates the power of molecular biology to produce structural and functional insights by uniting disparate fields such as bacterial nutrition and clinical endocrinology. The first union of the flytrap and the serpent was probably something of a shotgun wedding. But one of their offspring has evolved into a precisely machined and vital component of normal homeostasis in mammals. □

Bruce R. Conklin and Henry R. Bourne are in the Departments of Pharmacology and Medicine, and the Cardiovascular Research Institute, University of California, San Francisco, California 94143, USA.

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