ered metal is in the form of foil suggests that the material was used for its reflective properties and its ability to cover the surfaces of other materials; the addition of gold on one fragment further supports this view. Thus, it is likely that sheet metal was used to adorn people or ritual objects, to offer to the gods, or, flashing in the light, to impress audiences witnessing or participating in ceremonies.

To the ancients, natural forces, especially the sun with its life-giving rays that provided sustenance for humans, were more important than anything else, and metal that could capture and redirect light must have been seen as akin to fragments of the sun itself (*7*). Materials specialists Lechtmann (*8*) and Hosler (*9*) have both noted the emphasis on light, sound, and color in the creation of ornaments that included larger sheet-metal reflective disks and tinkling bells.

Curious creature. Gold snuff spoon in the shape of a monkey from Chavin.

Just as the energy of the sun is absorbed by all it touches, gold seems to have been thought of as imbuing other metals with its power (see figure). Thus, when alloying was elaborated in the New World, it occurred as much to infuse baser metals with the essence of gold as to provide structural properties to the objects produced. This seems to have been a distinctly Native American approach to metallurgy, just as some New World peoples valued the scent of gold alloys as much as or more so than the colors of these materials.

By the time of the arrival of the Spanish, Native American metal craftsmen rivaled their European counterparts in the sophistication of their technical skills, but the ideological and social constructs in which they worked were very different. Whereas the Spanish were caught up in the early stages of modern capitalism, for Native Americans, gold was of great value, but it was not a commodity; for some Americans, gold was considered the "feces of the gods," valuable to humans but, ultimately, the waste products of greater truth and beauty.

Although the earliest American metallurgy highlights both the differences and similarities and the value of metal working between the Old and New Worlds, its discovery and analysis underline our own value systems as citizens entranced with the tools of modern science. The work reported by Burger and Gordon, for example, required the use of sophisticated microprobe equipment. Yet the more fundamental scientific and human values of patience, care, and attention to detail are exemplified by the conduct of the authors of the report and their archaeological team. Less careful supervisors might have rushed their excavators to uncover more architecture at a faster rate, because large building plans are always impressive in archaeological reports. Such an approach might easily sweep away or overlook such tiny but important fragments. But in this case, as in so many others, slow and deliberate work and careful observation (very different from Hollywood's Indiana Jones) led to a remarkable discovery.

References

1. W. Alva and C. B. Donnan, *Royal Tombs of Sipán* (Fowler Museum of Culture History, University of California, Los Angeles, 1993).
2. J. Reinhard and S. Alvarez, *Natl. Geogr. Mag.* **188**, 90 (1996).
3. D. H. Sandweiss *et al.*, *Science* **281**, 1830 (1998).
4. R. L. Burger and R. B. Gordon, *Science* **282**, 1108 (1998).
5. C. Renfrew, *Before Civilization: The Radiocarbon Revolution and Prehistoric Europe* (Knopf, New York, 1979).
6. R. L. Burger and L. Salazar-Burger, *RES* **33**, 28 (1998).
7. N. J. Saunders, *ibid.*, p. 225.
8. H. Lechtmann, *Technol. Cult.* **25**, 1 (1984); in *Andean Art at Dumbarton Oaks*, vol. 1, E. H. Boone, Ed., (Dumbarton Oaks Research Library and Collection, Washington, DC, 1996), pp. 33–43.
9. D. Hosler, *The Sounds and Colors of Power: The Metallurgy of Ancient West Mexico* (MIT Press, Cambridge, MA, 1994).

PERSPECTIVES: ION CHANNELS

Exciting Times for PIP_2

Frances M. Ashcroft

Fats have many negative connotations in Western society, yet at the cellular level lipids and lipid metabolites are essential for cell function. Not only are they important structural components of cell membranes, they also generate—or even serve as—signaling molecules that mediate the action of hormones or transmitters. Two reports published in this issue on pages 1138 and 1141 (*1, 2*) add a further twist to the story by revealing a new role for membrane phospholipids in regulating the activity of the adenosine triphosphate (ATP)–sensitive potassium channel (K_{ATP} channel), a membrane protein that acts as a gated pore to control the movement of potassium ions into and out of the cell.

K_{ATP} channels are important in the physiology and pathophysiology of many tissues: in pancreatic β cells, they couple changes in blood glucose concentration to insulin secretion; in vascular smooth muscle they regulate vessel tone; and in cardiac tissue they are involved in action potential shortening during ischemia (*3, 4*). The channel derives its name from the fact that it is blocked by intracellular ATP, a molecule more widely known for its ability to power chemical reactions within the cell than as a channel regulator. One problem has puzzled people for years: why is K_{ATP} channel activity observed in the intact cell at cytoplasmic ATP concentrations that would be sufficient to inhibit the channel almost completely in an isolated membrane patch? The problem is particularly acute for the K_{ATP} channel of the β cell. Although this channel is half-maximally inhibited by an intracellular ATP concentration K_i of ~10 μM in excised patches, substantial channel activity is observed in intact β cells under conditions where measured cytosolic ATP is 3 to 5 mM (*3*), and estimates of the ATP sensitivity in the intact cell suggest a K_i of ~1 mM (*5, 6*).

Baukrowitz *et al.* and Shyng and Nichols suggest a solution to the puzzle (*1, 2*). They show that the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP_2) has a dramatic effect on the ATP sensitivity of the K_{ATP} channel. Addition of 5 μM PIP_2 to the cytosolic side of the membrane reduced the half-maximal inhibitory concentration of ATP from ~10 μM to more than 3 mM within 10 min (the slow time course presumably reflects progressive incorporation of the

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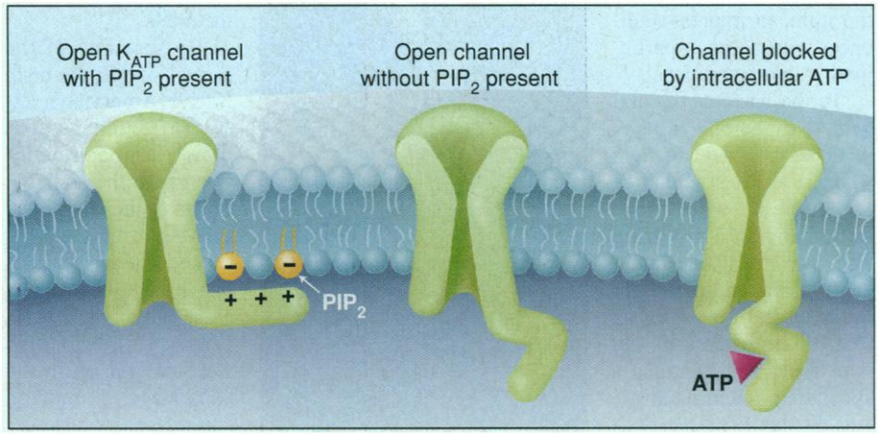
phospholipid into the membrane). The greater ATP sensitivity observed in isolated membrane patches might therefore be explained by the gradual loss of PIP_2 in excised patches, an idea that is supported by the increase in ATP sensitivity that begins immediately after patch excision (*1*). Loss of PIP_2 may occur, for example, due to the action of lipid phosphatases present in the membrane patch. The new results reported in this issue also solve another enigma: the wide variation in ATP sensitivity reported for K_{ATP} channels in the same tissue (*3*). It now seems likely that this is attributable to differences in the endogenous level of PIP_2 in the membrane.

The K_{ATP} channel is an octameric complex of $K_{ir}6.2$ and SUR subunits, with $K_{ir}6.2$ subunits forming the ATP-sensitive pore and SUR endowing sensitivity to channel regulators such as sulfonylurea drugs, K^+ channel openers, and Mg^{2+} nucleotides (*4*). Different types of K_{ATP} channel result from the association of $K_{ir}6.2$ with different kinds of SUR: SUR1 in β cells, SUR2A in heart, and SUR2B in smooth muscle. The activity of a number of other K_{ir} channels is regulated by PIP_2 (*7*), and so it is perhaps not surprising that PIP_2 interacts with the $K_{ir}6.2$ subunit of the K_{ATP} channel (*1*). Baukrowitz and co-workers present evidence that this regulation may be influenced by the presence of SUR (*1*), although the extent to which this occurs, the mechanism involved, and whether it depends on the type of SUR remain unclear.

PIP_2 binds directly to the cytosolic carboxyl-terminal domain of other types of K_{ir} channel, and binding is abolished by a mutation within this domain (*7*). Mutation of the equivalent residue in $K_{ir}6.2$ (R176A) reduced the rate at which PIP_2 was able to modify ATP inhibition (*1, 2*), suggesting that this residue may also form part of the binding site for PIP_2 in the K_{ATP} channel. Further support for the idea that PIP_2 interacts with $K_{ir}6.2$ itself comes from an experiment carried out by Shyng and Nichols (*2*). They found that a synthetic protein, corresponding to the carboxyl-terminus of $K_{ir}6.2$, reduced channel activity and that this inhibition was relieved by PIP_2. They therefore suggest that the synthetic protein competes with the carboxyl-terminus of $K_{ir}6.2$ for the phospholipid. These authors also explored which parts of the phospholipid molecule are required for reduction of ATP inhibition. They found that both a negatively charged head group and a lipid tail are needed, as neither inositol trisphosphate (which lacks the lipid tail) nor phosphatidylcholine (which lacks the negatively charged head group) were effective (*2*).

How does PIP_2 reduce the sensitivity of the channel to ATP? There are two obvious possibilities. First, PIP_2 might alter ATP binding, either by competing for the same, or overlapping, site on $K_{ir}6.2$ or by an allosteric effect on the ATP-binding site. In favor of this explanation is that the R176A mutation in $K_{ir}6.2$, which is associated with a reduced efficacy of PIP_2, lies close to residues implicated in channel ATP sensitivity (*8*). Confirmation of this idea requires competition binding studies: if ATP and PIP_2 interact with the same binding site (or overlapping sites), then it should be possible to displace ATP binding to $K_{ir}6.2$ with PIP_2, and vice versa. Such studies may also help define the ATP-binding site, which is currently unknown. The second possibility is that PIP_2 increases the negative surface charge of the membrane and reduces the concentration of the negatively charged ATP molecule at its binding site by electrostatic effects. This explanation is excluded by the competition experiments with the synthetic $K_{ir}6.2$ protein (*2*) described above. There is support, however, for the idea that surface charge is somehow involved in the action of PIP_2. Thus, positively charged ions, like polylysine and spermine, rapidly reduce the effect of PIP_2 (*2*) and enhance the efficacy of ATP (*9*). In addition, the ability of the phospholipid to reduce ATP inhibition increases with each additional negative charge; thus, PIP_2, with three negative charges, is more effective than PIP (which has two), and PI, which has only one, is ineffective (*1, 2*). The mechanism of action of PIP_2 is, therefore, more complex and may involve effects on surface charge, ATP-binding, and channel gating.



Not so sensitive. A model suggesting how PIP_2 may lower the sensitivity of the K_{ATP} channel to ATP. PIP_2 incorporates into the cell membrane where its negatively charged head group interacts with the carboxyl terminus of the K_{ATP} channel. This interaction distorts the ATP-binding site and prevents ATP from binding. When PIP_2 is not present, the channel is able to bind ATP, which causes it to close.

Many tantalizing questions remain. What is the resting concentration of PIP_2 in the cell membrane, and is it sufficient to account for the difference in the ATP sensitivity of the channel between the intact cell and the excised patch? Is the different metabolic sensitivity of β cell and cardiac K_{ATP} channels the result, at least in part, of different membrane levels of phospholipids? Do changes in PIP or PIP_2 levels contribute to the regulation of K_{ATP} channel activity by cell metabolism, or do phospholipids simply shift the set point about which metabolically induced changes in cytosolic nucleotides operate? Baukrowitz *et al.* (*1*) show that activation of the $P2Y_2$ receptor (which stimulates phospholipase C and lowers PIP_2) increases the ATP sensitivity of the K_{ATP} channel and so reduces the whole-cell current in heterologous systems. But does such regulation occur physiologically? Does defective regulation of K_{ATP} channel activity by PIP_2 contribute to the etiology of type 2 diabetes, in which the secretory response of the pancreatic β cell to glucose is impaired? Answering these questions definitively may take some time.

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References

1. T. Baukrowitz *et al.*, *Science* **282**, 1141 (1998).
2. S.-L. Shyng and C. G. Nichols, *ibid.*, p. 1138.
3. F. M. Ashcroft, *Annu. Rev. Neurosci.* **11**, 97 (1998).
4. F. M. Gribble and F. M. Ashcroft, *Trends Neurosci.* **21**, 288 (1998).
5. I. Niki, F. M. Ashcroft, S. J. H. Ashcroft, *FEBS Lett.* **257**, 361 (1989).
6. H. Schmid-Antomarchi, J. De Weille, M. Fosset, M. Lazdunski, *J. Biol. Chem.* **262**, 15840 (1987).
7. C. L. Huang, S. Y. Feng, D. W. Hilgemann, *Nature* **391**, 803 (1998).
8. S. J. Tucker, F. M. Gribble, C. Zhao, S. Trapp, F. M. Ashcroft, *ibid.* **387**, 179 (1997).
9. N. Deutsch, S. Matsuoka, J. N. Weiss, *J. Gen. Physiol.* **104**, 773 (1994).