The Canadian and Eurasian basins would be "coupled."

Furthermore, under the current atmospheric state, there are strong southerly winds over the Norwegian Sea, and hence the wind-driven inflow of warm Atlantic water into the Arctic is relatively strong, penetrating far into the central Arctic Basin (*11*). Any pollutants entering the ocean from Western Europe could thus penetrate far into the Arctic and might even reach the Canadian Basin. In contrast, during the 1950s to 1980s, when the three indices were mainly negative, the Atlantic inflow would not have penetrated very far into the Arctic Basin.

A useful perspective on the past history of the Transpolar Drift Stream has been provided by an analysis of Canadian Arctic Archipelago driftwood records for the past 8500 years (*12*), which showed that century-to millennial-scale changes in the Drift Stream must have occurred. A sea-ice model study (*13*) indicated that these changes are due to long-term changes in the phase of the NAO (and AO). In the model, the Drift Stream was relatively straight when the NAO was in a negative mode (similar to the blue curve in the second figure), whereas it followed a cyclonic path curved toward the Beaufort Sea when the NAO was positive.

It is clear that in response to atmospheric circulation fluctuations, the Arctic Ocean current and sea-ice drift patterns vary on a wide range of time scales. Gobeil *et al.* (*1*) were fortunate in analyzing sediments that accumulated over a period of several decades when the high-latitude atmospheric circulation was mainly in one (negative) state. It would be exciting to collect further sediment samples and redo their analyses some years after the atmospheric circulation has remained in the other (positive) mode to determine whether different flow pathways prevail.

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TRP Ion Channels—Two Proteins in One

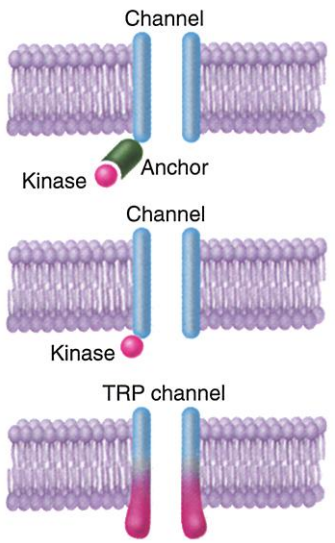
Irwin B. Levitan and Susan M. Cibulsky

It is no longer a rarity to come across a protein that performs more than one activity, but membrane ion channels do not seem to feature among these multifunctional proteins. However, a cluster of recent papers (*1–5*) reveal that two members of the long TRP (transient receptor potential) cation channel family—LTRPC7 and LTRPC2—are not only ion channels but also have enzymatic activity. LTRPC7 is both an ion channel and a protein kinase, and its kinase activity may influence its channel properties. Similarly, LTRPC2, an ion channel activated by ADP ribose (ADPR), has ADPR pyrophosphatase activity (*4, 5*). These intriguing findings—a surprise to many ion channel biologists—have important implications for the regulation of cell membrane excitability and for many other cellular processes in which ion channels participate.

Ion channels are a specialized class of membrane proteins that form hydrophilic pores through which ions move down their electrochemical gradients. The current carried by ions flowing through these membrane channels is responsible for such fundamental cellular phenomena as the resting membrane potential in all cells, the generation of action potentials in neurons, and neurotransmission at synapses. Ion fluxes through membrane channels also alter the intracellular concentration of ions, most notably Ca^{2+}, that influence signaling pathways. Channels, however, are far more than passive pores—they can shift rapidly back and forth between a nonconducting (closed) conformation and a conducting (open) conformation, a process known as channel gating.

The first member of the TRP channel family to be identified was a Ca^{2+}-permeable channel responsible for the depolarization of *Drosophila* photoreceptor cells in response to light. This channel opens when phospholipase C activity increases, which in turn is stimulated by light-activated rhodopsin in the photoreceptor cells. Numerous TRP channels are now known, and many of them are associated with the transmission of sensory information (*6*). Members of one subfamily, the long TRP channels, have an extended carboxyl-terminal domain at the end of the predicted membrane-spanning portion of the protein, and their gating is not well understood.

Reports by three separate groups (*1–3*) describe the cloning and characterization of LTRPC7 (also called ChaK or TRP-PLIK), a new member of the long TRP channel family that exhibits both ion channel and protein kinase activities. LTRPC7 is expressed widely in mouse tissues (*1*) and is crucial for cell survival (*2*). When LTRPC7 is expressed in cultured cells, single-channel and whole-cell currents characteristic of TRP channels can be readily recorded (*1, 2*), leaving no doubt that LTRPC7 is an ion channel. Intriguingly, the extended carboxyl-terminal domain of LTRPC7 contains a region with sequence similarity to certain serine-threonine protein kinases of the atypical α-kinase family. Indeed, this region of LTRPC7 does have protein kinase activity and is capable of phosphorylating the channel itself as well as at least one other substrate (*1*). Another surprise comes from the three-dimensional structure of the kinase domain, solved by x-ray crystallography (*3*). The structure of its catalytic core closely resembles that of more classical protein kinases (typified by the cAMP–dependent protein kinase, PKA) even though



Ion channel or enzyme? (Top) An ion channel (blue) may associate with a protein kinase (red) with the help of an intermediary anchoring protein (green). **(Middle)** Alternatively, an ion channel may physically interact with a protein kinase directly. **(Bottom)** Two ion channels, LTRPC7 and LTRPC2, have been identified with both channel and enzyme activities within the same protein.

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classical kinases share essentially no sequence similarity with LTRPC7 or other atypical α-kinases. Several amino acid residues known to be crucial for catalysis in PKA are conserved in LTRPC7, and the locations of these residues within the kinase domains of PKA and LTRPC7 are similar. There are, however, structural differences between the two kinase domains. For example, LTRPC7 contains a zinc-binding motif not present in classical kinases, which is predicted to be important for the structural stability of the kinase catalytic domain. Mutations in this motif markedly reduce LTRPC7 kinase activity, consistent with the structural evidence that it is important for catalysis. A key question is whether kinase activity is important for operation of the LTRPC7 channel. Although Runnels *et al.* (*1*) present evidence that kinase activity is essential for channel gating, this conclusion has been challenged by Nadler *et al.* (*2*), and the controversy has yet to be resolved.

Ion channels, like so many other cellular proteins, are regulated by protein phosphorylation and dephosphorylation (*7, 8*). The idea that protein kinase and phosphoprotein phosphatase activities might be associated with ion channels is not new. Kinase activity has been detected in some purified ion channel preparations (*9, 10*), and functional experiments also suggest that kinase and phosphatase activities are intimately associated with the gating of certain channels (*11–15*). More recent biochemical and molecular approaches have made it clear that channels can associate with protein kinases and phosphatases, either with the help of anchoring or scaffolding proteins (*16–19*) or directly (*20–24*). What is most exciting about the new studies is the possibility that channel and kinase activities are intertwined because they are both encoded in the sequence of a single protein (see the figure). It would appear that evolution has chosen a variety of ways to ensure that these activities remain together.

Apparently, LTRPC7 is not the only example of an ion channel with enzymatic activity. LTRPC2, another member of the long TRP channel family, contains ADPR pyrophosphatase activity (*4*) and its gating is controlled by intracellular ADPR (*4, 5*). Like LTRPC7, LTRPC2 is a cation channel expressed by many different tissues. Here again, there is some controversy about channel gating. Both groups studying the gating of LTRPC2 agree that ADPR activates (opens) the channel. On the other hand, nicotinamide adenine dinucleotide (NAD), a precursor of ADPR, is described by Perraud *et al.* (*4*) as having no effect on channel activation, but by Sano *et al.* (*5*) as causing delayed channel activation when included in the whole-cell recording pipette. The interpretation of these results is complicated by the fact that NAD can be metabolized to ADPR, and hence the exact effect of NAD on LTRPC2 channel activation remains unclear. The identification of pyrophosphatase activity specific for ADPR within the carboxyl-terminal region of LTRPC2 suggests that this channel may have evolved an enzymatic activity that limits the availability of its physiological activator, rather than one that promotes its activation, as may be the case for LTRPC7.

Where does the field go from here? These are unlikely to be the last reports of enzymatic activity in ion channel proteins. For example, where there is a protein kinase there is often a phosphatase lurking nearby, and it would come as no surprise to find that some ion channels have phosphatase activity. Finally, the intimate association of enzymatic activities with ion channels raises the intriguing question of whether the ions that flow through the channel—or the conformational changes associated with channel gating—may contribute to the regulation of the enzyme. In other words, are the long TRP channels examples of ion channels with their own personal modulatory enzymes, or are they enzymes that are regulated by their own personal ion channels? Perhaps they are both. Stay tuned for the answer.

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PERSPECTIVES: NEUROBIOLOGY

Learning How a Fruit Fly Forgets

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Whether in humans or fruit flies, memories must be acquired, stored, and retrieved. Although these three stages are separate, distinguishing between them experimentally is tricky. A report by McGuire *et al.* on page 1330 of this issue (*1*) and another published in *Nature* by Dubnau *et al.* (*2*) provide a convincing dissection of olfactory memory in the fruit fly *Drosophila*. With the help of a temperature-sensitive *shibire*^{ts1} (*shi*^{ts1}) transgene, both groups conclude that synaptic output from structures in the fly brain called mushroom bodies (MBs) is required for recall of olfactory memory but not for its acquisition or storage.

The *shibire* gene encodes dynamin, a mictrotubule-associated guanosine triphosphatase that is important for synaptic vesicle recycling in neurons and hence for synaptic transmission (*3*, *4*). The temperature-sensitive allele *shi*^{ts1} encodes a version of dynamin that is defective if the temperature is raised above 29°C (the restrictive temperature). When *shi*^{ts1} flies are exposed to the restrictive temperature, synaptic vesicles can no longer be recycled and synaptic transmission throughout the central nervous system ceases (*5*). The *shi*^{ts1} allele was originally identified in flies that became paralyzed at the restrictive temperature (because neural activity was blocked) but moved normally at the permissive temperature (20°C) (*6*). If the cause of paralysis is restricted to a known subset of neurons, then the involvement of these neurons in specific behaviors can be tested (*7*). For example, expression of a *shi*^{ts1} transgene in fly photoreceptor neurons causes blindness at elevated temperature (30°C) and expression of the same transgene in cholinergic neurons causes paralysis at this temperature. These handicaps are quickly reversed if the flies are returned to a lower temperature (20°C).

Fruit flies learn to avoid an odor that is administered in association with an electric shock (*8*), and such learning depends on the MBs. Flies that lack MBs can smell odors and sense electric shocks, but they

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