By contrast, the large Oligocene regression was not accompanied by excessive extinctions among shallow-water organisms. "If the species-area effect were ever to have devastated species of shallow-water marine benthos globally, it should have done so at this time."

Looking to mass extinctions earlier in the geological record, Stanley believes he can make an argument for associated global refrigeration in most cases, and this includes that most notorious of mass extinctions, the Cretaceous/Tertiary boundary 65 million years ago, which, among other things, saw the demise of the dinosaurs.

The connection between extinction and refrigeration events is not always easy to make, however, partly because of the problems of inferring temperature regimes far back into the record, and partly because of a distinction that has to be made between polar and global refrigeration. Although polar glaciation might appear to be a potentially dramatic occurrence, it can in fact be rather localized, so that the tropics are little affected.

By contrast, general global cooling of an earth that has equilibrated to a balmy climate with gentle temperature gradients between the poles and equator could have a devastating effect, particularly in the tropics. Many organisms on such an earth would be adapted to a narrow range of temperatures, so even a slight cooling would initiate a squeeze to the tropics, with casualties lost in geographic traps. This pattern—of a balmy world being particularly vulnerable to even slight cooling—might seem somewhat counterintuitive.

Although some species are able to tolerate a wide range of environmental conditions and therefore potentially can be geographically widespread, many must remain within narrow limits, which is known as stenotopy. In Stanley's view—supported here by Kauffman—stenotopy is in large measure stenothermy, or narrow temperature tolerance. This, combined with the known climatic fluctuations that have tracked Earth history, must imply that episodes of cooling have a strong potential as a proximal agent of occasional mass extinction. Whether it is *the* agent in the markedly periodic history of life remains to be proved. As Hallam cautions—and Stanley would agree—"No one can afford to be dogmatic about anything yet."

—**ROGER LEWIN**

Additional Reading

Mass Extinctions, Matthew H. Nitecki, Ed. (University of Chicago Press, Chicago, to be published in May 1984).

Receptor Reconstituted

The purification of the β-adrenergic receptor protein is opening new ways of studying how this important receptor mediates the responses of cells to catecholamines, the physiological activators of the receptor. Robert Lefkowitz, Marc Caron, and their colleagues at Duke University Medical Center have reported that the purified protein can be inserted into the membranes of cells that ordinarily lack the receptor, conferring on them the ability to respond to a catecholamine.* "The molecule does all the things one thought a receptor should do," Lefkowitz says.

About a year ago, Lefkowitz and his colleagues purified the β-adrenergic receptor of frog erythrocytes; it turned out to be a single protein chain with a molecular weight of 58,000. More recently, they purified the receptors from hamster and guinea pig lungs. Each of these receptors also consists of a single protein chain, but the molecular weight is higher, 64,000.

Receptors must both bind to their ligands with appropriate specificity and also evoke a response in the cell. Although ligand binding can be studied with a purified receptor, the cellular consequences of the binding cannot. The β-adrenergic receptor must activate the enzyme adenylate cyclase to produce the "second messenger," cyclic AMP, to bring about its effects on the cell. "Our group had shown that we could purify a molecule with all the basic binding characteristics of a β-adrenergic receptor," Lefkowitz says. "But did it also contain the machinery for activating the adenylate cyclase?"

As the first step to answering this question the Lefkowitz group incorporated the purified protein into phospholipid vesicles. They then fused the vesicles with red blood cells of the African clawed toad, which have few or no β-adrenergic receptors of their own. However, they do have the other proteins needed for the cyclic AMP response. After fusion with vesicles containing a β-adrenergic receptor protein, the red blood cells gained the ability to respond to a catecholamine by producing cyclic AMP. Martin Schramm and his colleagues at Hebrew University in Jerusalem and Steen Pedersen and Elliott Ross of the University of Texas Health Science Center in Dallas had previously shown the feasibility of such reconstitution experiments but had used unpurified receptor preparations.

The experiments by the Lefkowitz group show that a single protein chain performs both the ligand-binding and cyclase-activating functions of the β-adrenergic receptor. This receptor appears simpler than the others that have been characterized so far. The receptors for insulin, acetylcholine, and immunoglobulin E are composed of multiple subunits.

The β-adrenergic receptor, an important regulator of the circulatory and respiratory systems, is a frequent target of therapeutic drugs. The ability to reconstitute the receptor response with purified protein opens the way to studying such problems as drug desensitization, Lefkowitz says. Cells frequently lose their responsiveness to a receptor activator, whether it be the endogenous one or a drug mimic, after varying periods of exposure. Densensitization can be a problem in the treatment of many conditions, including asthma.

Often the diminished responsiveness is caused by an actual decrease in the number of receptors in the membrane. But it can also be caused by a reduced effectiveness of the receptor in activating the cellular response. The Lefkowitz group found that the β-adrenergic receptor of turkey erythrocytes, when exposed to catecholamines, loses its ability to activate adenylate cyclase. This change appears to be caused by phosphorylation of the receptor, perhaps by the protein kinase that is activated by cyclic AMP.

In any event, it will now be possible to isolate the receptor from desensitized cells and see how effectively this protein works in the reconstitution assay. Or the protein can be modified in defined ways to study its interactions with the other components needed to activate the cells. "If we understand desensitization, it might be possible to develop ways to interdict it," Lefkowitz notes.—**JEAN L. MARX**

*R. A. Cerione, B. Strulovici, J. L. Benovic, R. J. Lefkowitz, M. G. Caron, *Nature (London)* **306**, 562 (1983).