fornia's Lawrence Berkeley Laboratory (LBL) and the Joint Institute for Nuclear Research in Dubna, U.S.S.R., have been scooped. As soon as more material becomes available, according to Albert Ghiorso of LBL, these laboratories and others will engage in a race to explore the properties of these superheavy elements and to create new ones by bombarding the monazite in accelerators.

Finding superheavy elements in monazites, which were formed early in the earth's history, raises at least two questions for nuclear scientists. Calculations based on a synthesis of the liquid drop and shell models of the nucleus had indicated that element 126, for example, would decay by alpha emission with half-lives from a few nanoseconds to about a thousand years, depending on the number of neutrons, according to J. Rayford Nix of the Los Alamos Scientific Laboratory in New Mexico. But the geologic age of the earth is 4.5×10^9 years.

The short half-lives expected are due to the large electrostatic repulsion between protons which overcomes the attractive nuclear forces and makes spontaneous fission of nuclei more and more likely as their atomic numbers rise above 100. The probability of radioactive decay by emission of alpha particles also increases as coulomb forces become stronger. The shell model of the nucleus, whereby the protons and neutrons are arrayed in shells somewhat like atomic electrons, provides a way to circumvent these instabilities under certain circumstances.

When the proton and neutron shells are filled, a barrier to fission large enough to permit lengthy nuclear lifetimes occurs. The "magic number" for which this closed shell condition would hold was thought to be 114 protons and 184 neutrons. But all calculations of nuclear lifetimes are based on extrapolations of models known to fit much lower mass nuclei. Thus, calculating the stability of superheavies is a tricky business.

By making only small changes in the parameters used in a model such as Nix's, theoreticians can effect changes in nuclear lifetimes of several orders of magnitude, according to Fred Petrovich at FSU. Looked at from this point of view, the new superheavy elements provide a guidepost for assigning values to parameters which were heretofore selected on the basis of incomplete information.

A second problem for theoreticians has to do with whether the putative superheavy elements were created by the processes of nucleogenesis in stars. The most important of these for heavy elements is the r-process in supernovas, which involves a sequence of multiple capture of neutrons to increase the nuclear mass followed by emission of electrons to increase the atomic number. Calculations based on the liquid drop model of the nucleus had led theorists to believe that spontaneous fission would interrupt this process before superheavy elements could be formed, according to Nix. Moreover, the details of the giant halos are such that it is possible that they were caused by alpha decay of even heavier elements than those apparently now residing in the monazite inclusions, say the experimenters, and thus would be much harder to produce.

For now, the most important thing, all agree, is to verify the existence of superheavy elements. The ORNL-FSU-UCD team is now working to improve their data by correcting the tendency of the Van de Graaff beam to wander away from the inclusion. But, if further x-ray evidence proves inconclusive, a number of scientists who are waiting in the wings with other physical and chemical tests involving separation, concentration, or nuclear bombardment of superheavy elements would be only too happy to have a crack at the new elements.

—ARTHUR L. ROBINSON

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Hormone Receptors: New Clues to the Cause of Diabetes

Diabetes is commonly thought of as a disease in which the pancreas produces insufficient quantities of the hormone insulin. For about 10 percent of American diabetics, who suffer from the juvenile-onset form of the disease, that is, in fact, the case. But for the vast majority, who suffer from maturity-onset diabetes, the pancreas produces normal quantities of insulin—and, in many cases, quantities that are well above normal. The problem is, rather, a reduced sensitivity of fat and muscle cells to the effects of insulin, a phenomenon commonly referred to as insulin resistance.

The cause of this insensitivity is still unknown. But a significant increase in understanding of the fundamental defect of diabetes has evolved in the past 3 years. The principal catalyst for this progress was the identification of specific sites on cellular membranes where insulin and glucagon interact with the cell to regulate glucose metabolism. Identification of these receptors has provided a major new tool for study of the basic causes of diabetes. This tool has so far made possible the discovery that binding of both insulin and glucagon to many types of cells is much lower than normal in both diabetics and insulin-resistant obese individuals. It has also shown that insulin binding can be returned toward normal by regulation of the diet and by certain drugs. Some evidence further suggests that screening for reduced insulin binding can identify individuals who are likely to develop diabetes.

Direct studies of the insulin-receptor interaction with the use of radioactively labeled insulin were first attempted in 1949 by William C. Stadie of the University of Pennsylvania, but severe technical difficulties were encountered. The problems included the extremely small amount of hormone that binds to the receptor, uncertainty about whether the labeled hormone was biologically active, and complications resulting from nonspecific binding. The problems were largely resolved by 1969, when two groups of investigators independently solved the problems and made the first clear identification of hormone receptors. Ira H. Pastan of the National Cancer Institute, Jesse Roth of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), and Robert J. Lefkowitz, now at the Duke University School of Medicine, identified the receptor for adrenocorticotropic hormone (ACTH). And S.-Y. Lin and Theodore L. Goodfriend of the University of Wisconsin identified the receptor for angiotensin.

The techniques developed by these investigators have proved applicable to all the polypeptide hormones, each of which has a receptor in the cell mem-

brane of target tissues. Within the last 5 years, consequently, receptors for at least 12 different polypeptide hormones have been identified and characterized and, in some cases, isolated and partially purified. Two of the receptors that have been isolated are those for insulin and glucagon.

Insulin and glucagon are antagonistic hormones that regulate the metabolism of glucose. Insulin mediates the uptake of glucose by liver, muscle, and fat cells and the conversion of glucose to glycogen within those cells. Glucagon mediates the transfer in the opposite direction. Glucagon is apparently always present in higher than expected concentrations in diabetics, but insulin may be present in normal, higher, or lower concentrations, depending on the type of diabetes. In most forms of maturity-onset diabetes, it is present in higher than normal concentrations. The importance of glucagon in diabetes has only been recognized within the past 2 or 3 years (*Science*, 30 May 1975, p. 920). The insulin receptor is much better characterized than the glucagon receptor.

Insulin Receptor Isolated

The insulin receptor was first isolated in 1971 from rat liver membranes by Pedro Cuatrecasas and his associates at the Johns Hopkins University School of Medicine. The isolation was relatively difficult because insulin exhibits spurious binding to many substances. Cuatrecasas, who is now at the Burroughs-Wellcome Company in Research Triangle Park, North Carolina, notes that it binds to glass, talc, silica, and many other substances with kinetics which suggest that it is binding to a specific receptor. This binding is very difficult to distinguish from binding to a specific receptor, and often can be distinguished from genuine binding only by quite complicated technical procedures. The isolation of hormone receptors is thus a very tedious procedure in which great care must be taken to ensure that binding studies used to monitor the purification are not measuring artifacts.

There are two other major problems in isolating the receptors. The receptors are intimately embedded in the cellular membrane, and they are present only in very low concentrations. The first problem is overcome by disrupting the membrane with a detergent, which not only frees the receptor from the lipid matrix but also makes it soluble in the aqueous solutions used for further purification.

The second problem has been solved by Cuatrecasas and other investigators by means of affinity chromatography. In this technique, the hormone or a derivative of it is attached to an insoluble polymer in such a fashion that binding to the receptor is not impaired. When a subcellular preparation containing receptors is passed through a column containing such a polymer, the receptors will bind to the polymer and stay in the column while other components simply pass through.

Employing a combination of ion exchange chromatography and affinity chromatography, Cuatrecasas now has achieved a 250,000-fold purification of insulin receptors. He estimates that a 400,000-fold purification would give absolute purity. For his effort, he has obtained a very small quantity of a glycoprotein with a mass of about 300,000 daltons. The insulin-binding characteristics of this glycoprotein are identical to those of the receptor in the intact membrane. Further physical characterization of the receptor, however, will require substantially larger quantities. Cuatrecasas has observed that unusually high concentrations of the receptor are present in human placentas, and he is currently isolating larger quantities of receptors from that source.

Glucagon Receptors

Similar procedures were used by Melvin Blecher, Nicholas A. Giorgio, and Carl B. Johnson of the Georgetown University Medical Center to isolate glucagon receptors from rat liver membranes. They have achieved a 3000-fold purification of the receptors to obtain a glycoprotein that is nearly as pure as that of Cuatrecasas. (The extent of purification is not necessarily indicative of the absolute purity of the preparation, but rather of its initial concentration in the tissue. Equally pure acetylcholine receptors can be obtained from eel tissue with only a 500-fold purification.) The glucagon receptor has a mass of about 190,000 daltons, and its binding characteristics are also nearly identical to those of the receptors in intact membranes. The physical characteristics of the glucagon receptor are still being delineated.

Further studies of the receptors should provide a great deal of information about the mechanisms of insulin and glucagon action and about the nature of cellular control mechanisms. So far, however, much of the work on receptors has been devoted to quantifying their concentrations in various tissues. Insulin and glucagon receptors have been identified in liver, fat, and muscle cells in rodents and humans and in heart cells in rodents. They have also been found in two types of white blood cells—monocytes and granulocytes—in humans. Neither hormone was thought to have a function in white cells, so their presence there is somewhat of a surprise. But it is a fortuitous surprise because the white cells are readily accessible for the study of receptors in humans.

Genetically Obese Mice

The majority of the studies of insulin binding have been conducted with genetically obese mice, which exhibit an insulin resistance similar to that observed in maturity-onset diabetes. Many of these studies have been conducted by Roth, C. Ronald Kahn of NIAMDD, and Pierre Freychet, now at INSERM in Nice, France. Many of the recent studies with obese humans and diabetics have been conducted by Jerrold M. Olefsky and his associates at the Stanford University Medical Center.

Both groups of investigators have found that there are reduced numbers of insulin receptors in insulin-resistant tissues from rodents and humans. Roth finds, for example, that liver membranes from obese mice bind only about 35 percent as much insulin as membranes from lean mice, and that this reduced binding is a direct result of a reduced number of receptors. Similarly, Olefsky and Gerald M. Reaven of the Stanford University School of Medicine have shown that monocytes from maturity-onset diabetics bind only about 50 percent as much insulin as monocytes from healthy individuals, and that there are only about 1200 receptors per monocyte from diabetics compared to 2200 per monocyte from healthy subjects. Cuatrecasas has observed that there are also reduced numbers of receptors for plant lectins in such cells, and he suggests that there may be a decrease in the total amount of glycoproteins in the membrane.

Roth, Kahn, and Olefsky have observed a strong inverse correlation between the concentration of insulin circulating in the blood and the number of insulin receptors. That is, the greater the concentration of circulating insulin, the lower the number of insulin receptors in liver, fat, muscle, and blood cells.

The correlation holds for healthy rodents, genetically obese rodents, rodents fed gold thioglucose (which destroys the appetite control center in the brain to produce gross overeating and weight gain), and obese rodents "dieted back"

to normal weight. It also holds for healthy humans, obese humans, and humans with maturity-onset diabetes. It does not hold for rodents and humans when the ability of their pancreases to secrete insulin has been lessened by drugs or other agents, as in the case of juvenile-onset diabetes. With this restriction, there are only three important exceptions to the correlation, and the significance of these is not yet clear.

Change in Diet

Lester Salans and Samuel Cushman of Dartmouth University have reported that the level of circulating insulin in mice is increased when they are fed a diet high in carbohydrates. This increase is not accompanied by a reduction in the number of receptors. Olefsky argues, however, that the increase in insulin occurs only after the meals, and that the basal concentration of insulin in mice fed such a diet is actually somewhat lower than normal. This decreased basal concentration, he contends, is much more important than transient increases in regulation of the number of receptors.

The most important point of controversy involves the number of receptors in large fat cells (adipocytes) from animals and humans. Cuatrecasas and Dean H. Lockwood, John M. Amatruda, and James N. Livingston of the Johns Hopkins University School of Medicine find no reduction in the number of insulin receptors in large adipocytes from obese mice and obese humans. They find that there are about the same number of receptors in large adipocytes from obese rats as there are in small adipocytes from lean rats. Lockwood also finds that there is no difference in glucose transport between the two types of cells, indicating that there is no defect in insulin binding in the large adipocytes.

Cuatrecasas and Steven Jacobs of Burroughs-Wellcome have developed a mathematical model for the cellular membrane which postulates that the receptors are very mobile in the plane of the membrane. This model requires that a receptor, after occupation by the hormone, must interact or aggregate with another membrane protein, called the effector, before the signal from insulin binding can be transmitted to the interior of the cell. This model suggests other possible abnormalities of receptor function—for example, that the increased average distance between receptors and effectors in the membrane of the large adipocytes may impair the transmission of the signal from insulin and produce insulin resistance.

Olefsky, in contrast, finds that there is a decrease in the number of insulin receptors in large adipocytes. He and Roth, furthermore, argue that insulin binding is a membrane phenomenon, so the most important characteristic is the number of receptors per unit area of membrane. When the data of Lockwood and Cuatrecasas are interpreted in this manner, Roth says, their results agree much more closely with his and Olefsky's. Both Lockwood's and Olefsky's results have apparently been confirmed by other investigators, so it is not yet clear which interpretation is most accurate. In any case, insulin metabolism in adipocytes plays only a small part in the total insulin metabolism of obese individuals, and its role in diabetes may be even less important.

The third apparent deviation from the insulin-receptor correlation is less easily resolved. Blecher and Steven Goldstein of the Georgetown University Medical Center studied insulin binding to human monocytes. Their results with monocytes from healthy individuals and from maturity-onset diabetics agree very closely with those of other investigators. Surprisingly, however, they also found that there was reduced binding of insulin to monocytes from 11 individuals classed as prediabetics—that is, individuals from families where one parent was a maturity-onset diabetic. This reduced binding was observed even though there were no other symptoms of diabetes and, in particular, no increase in levels of circulating insulin.

Screening for Diabetes

Blecher argues that his results suggest that the prediabetics whom he and Goldstein examined are quite likely to develop diabetes. He contends that the test for insulin binding to monocytes could thus be adapted for use as a screening test to identify individuals who are most likely to develop diabetes. Once identified, those individuals could then presumably regulate their diet and weight to prevent or, at least, delay the onset of the disease.

Other investigators do not completely agree with him. For one thing, this is the only relatively clear-cut case where a reduced number of insulin receptors is not accompanied by a correspondingly high level of circulating insulin. Furthermore, only a minority of the offspring in families where one parent is diabetic can be expected to become diabetic themselves, whereas Blecher and Goldstein have observed reduced numbers of receptors in all the offspring they have examined. Their results thus do not mesh with any current theory of insulin-receptor interaction, and other investigators view the results with some suspicion. In any case, studies on insulin binding in a much larger group of prediabetics will be required before any firm conclusions can be drawn about what is happening.

Glucagon binding has been studied to a much lesser degree. Livingston and Lockwood have shown that large adipocytes from obese mice bind less glucagon than adipocytes from lean rodents. Vincent Manganiello and Martha Vaughn of the National Heart, Lung, and Blood Institute have made a similar observation. And Blecher and Goldstein have shown that there is reduced binding of glucagon to monocytes from obese humans, maturity-onset diabetics, and prediabetics. But the relationship of the number of receptors to concentrations of glucagon in the blood and the significance of this relationship in the disease state have been largely unexplored.

Insulin Receptors and the Disease State

The significance of the observations on insulin receptors with respect to the disease state is not yet clear. If it is granted that the correlation between insulin levels and receptors holds for most individuals, the obvious question then becomes: Which is cause and which is effect? A growing body of evidence indicates that the increased concentrations of circulating insulin may be the cause and the reduced number of receptors the effect.

Roth, James R. Gavin III, and their associates at NIAMDD have shown, for example, that incubation of cultured human lymphocytes in the presence of higher than normal concentrations of insulin leads to a reduction in the number of receptors. Cuatrecasas and Kwan-Jen Chang of the Johns Hopkins University School of Medicine have confirmed this result. But the two investigators have different explanations for their observations.

Cuatrecasas points out that Peter Rieser of the University of Louisville School of Medicine has shown that insulin has inherent proteolytic activity; that is, it is able to catalyze the breakdown of proteins. Cuatrecasas has also shown that insulin receptors are particularly sensitive to proteolytic enzymes, that the effect is observed with analogs of insulin that do not bind to the receptors, and that the effect is seen even in cells that are for all practical purposes dead. This and other evidence, he argues, suggests that insulin may directly catalyze the breakdown of insulin receptors.

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Roth, however, argues that the effect is part of a more complex regulatory mechanism. He contends that the observed proteolytic activity of insulin is much too small to account for the observed decrease in receptors. He finds, furthermore, that the insulin must bind to the receptor before the effect is observed, and that anything which disturbs the normal functioning of the cell—such as a reduction in temperature, inhibition of energy production, or inhibition of protein synthesis—stops the loss of receptors. Roth thus argues that high concentrations of insulin somehow provoke an acceleration of loss of receptors. This feedback control prevents the cell from being overstimulated by the large amounts of hormone that are present. Similar regulatory mechanisms, he adds, have now been observed for other hormone-receptor systems. Many of Roth's and Cuatrecasas's observations are obviously in direct conflict, and the source of this conflict is not yet clear.

A Change in Equilibrium

But reducing the number of receptors does not provide precisely the same equilibrium, Roth argues, and glucose metabolism becomes slightly deranged. The greater the reduction in number of receptors, furthermore, the greater the degree of derangement. This possibility, he concludes, suggests the need for a reappraisal of the manner in which insulin is used therapeutically.

Perhaps one of the most important observations from the study of receptors is the recognition that the concentration of circulating insulin and the number of receptors can be controlled by diet. Roth, Phillip Gorden of NIAMDD, and Juanita A. Archer of Howard University made a study of insulin binding in 11 obese individuals. Their findings were consistent with other studies in that insulin concentrations were high and the number of receptors in monocytes was low. They also found, however, that restricting the caloric intake of the subjects produced a reduction in insulin concentrations and an increase in the number of receptors. The return to normal occurred with only a modest weight loss. Blecher and Goldstein have similarly observed normal binding of insulin and glucagon to monocytes from three obese diabetics who were following a rigid diet. And Olefsky and others have observed the same effects in rodents.

This finding could have major implications for maturity-onset diabetics—80 percent of whom are overweight. Roth's results, in particular, indicate that a major cause of insulin resistance—and thus of derangements in glucose metabolism—in these individuals is overeating. This suggests that much better control, and perhaps even complete control, of diabetes can be achieved by close regulation of the diet. This possibility is buttressed by the results of several clinicians, such as Jack H. Davidson of the Emory University School of Medicine, who have demonstrated that most maturity-onset diabetics can control the disease by regulation of their diet. This approach may receive even more attention in the future as a result of growing disenchantment with use of drugs and insulin for control of diabetes.

Oral Agents Increase Binding

Oral antidiabetic agents such as the sulfonylureas also have a surprising effect on insulin binding. Olefsky and Reaven have found that monocytes from untreated, nonobese, maturity-onset diabetics who exhibited fasting hyperglycemia had a reduced number of insulin receptors. When these subjects were treated with the sulfonylurea chloropropamide, Olefsky and Reaven observed, their fasting hyperglycemia was reduced and the number of insulin receptors increased, although neither returned to normal. Previous studies have shown that chloropropamide does not alter insulin secretion, and Olefsky and Reaven's evidence indicates that it does not interact directly with the receptors. It thus seems likely that the drug in some manner affects the control mechanisms that regulate the number of receptors.

There are, of course, probably other defects associated with maturity-onset diabetes and obesity. This is almost certainly the case with the large adipocytes, where most of the investigators agree that the principal defect lies in the intracellular metabolism of glucose. This may also be the case with some of the more severe forms of maturity-onset diabetes. But for the majority of the cases of maturity-onset diabetes, which involve mild symptoms in association with obesity, a majority of the investigators might now agree that one of the major causes is a defect in insulin binding to receptors on the cell surface.

—THOMAS H. MAUGH II

Erratum. An article about plant biochemistry in the Research News section of the 28 May issue of *Science* made reference to "the late K. Müller of Germany." Müller is alive and well, and *Science* regrets any problems that might have arisen from this mistake.