EDITORIAL

THE SIGNIFICANCE OF THE ACTION OF INSULIN UPON MUSCLE MEMBRANE POTENTIAL

Two observations placed in juxtaposition may clarify the mechanism of action of insulin. The first is that insulin in contact with intact rat muscle causes net movement of potassium from extracellular fluid into muscle. The second is concerned with the electrical potential difference across the cell membrane of resting muscle which depends in part upon the relative concentrations of potassium on either side of the membrane. Let us consider these observations, beginning with the second.

Using an appropriate apparatus, it can be shown that there is a potential difference between electrodes placed inside and outside a muscle fiber. This means that the membrane is polarized. The inside of the fiber is negative. The potential varies in different preparations. In excised frog muscle[1] and in leg muscles in situ in adult rats,[2] the resting membrane potential, E_R, is about —90 mV. In excised leg muscles of immature rats E_R is generally between —70 and —75 mV.[3]

Nernst developed a relation between the ion concentrations of two conjoined solutions of a common electrolyte and the electrical potential difference between them. Later Donnan arrived at an expression identical to Nernst's. In the system used by Donnan, the presence of a nondiffusible ion displaces diffusible ions so that at equilibrium the concentrations of each species of diffusible ion on the two sides of the membrane are unequal. As a result of inequality of ion concentration there must be a potential difference across the membrane. The size of the potential is predicted by the product of a temperature-dependent constant and the logarithm of the ratio of the concentration of any one of the diffusible ions on one side of the membrane to its concentration on the other side, viz.

$$E = \text{constant} \times \log \frac{I_i}{I_o}$$

Höber[4] and Bernstein[5] were probably the first to apply these proposals from physical chemistry to examination of potentials in living systems. They reasoned that the high concentration of potassium inside cells, compared to its low concentration outside, might account for the observed high injury potentials.

After so fruitful a beginning the matter rested for several decades owing to lack of refined technics for measuring potentials. Around 1940 Cole and Curtis[6] made precise measurements by impaling the giant axon of the squid with an electrode. Interest in the relation between ion concentrations and bio-electrical phenomena was revived.

Boyle and Conway[7] predicted from Donnan's equations that the product of potassium and chloride concentrations in muscle-fiber water should equal the same product in extracellular water. From their measurements in frog muscle they concluded that these substances did indeed behave as though muscle were a Donnan membrane system. It might be hoped, then, that E_R could be explained entirely by the Donnan phenomenon.

So simple an explanation, however, is not quite tenable. Both the Nernst and the Donnan treatments of simple solution systems assume equilibrium conditions. E_R is not completely described either by the predicted equilibrium potassium potential or by the predicted equilibrium chloride potential. The calculated potassium equilibrium potential in frog and in rat muscle is about —100 mV, a value uniformly higher than the observed value, E_R.

Despite the complexities of interpreting E_R quantitatively in terms of ion concentrations when these are normal, there is no doubt that when extracellular potassium concentration is raised enormously, say by tenfold or more, E_R in excised nerve and muscle can then be described fairly accurately by the product of a constant and the logarithm of the ratio of intracellular to extracellular potassium concentrations.[1,6] Either an increase in extracellular potassium concentration or a decrease in intracellular potassium concentration decreases the ratio of concentrations and decreases the membrane potential; the membrane is hypo- or depolarized. An increase in intracellular or a decrease in extracellular potassium concentration increases the ratio of concentrations and increases the membrane potential; the membrane is hyperpolarized.

With this background, we can return to the second observation: Insulin produces a net movement of potassium into muscle. In the intact animal in which intracellular potassium mass is very large compared to extracellular potassium mass, net movement of potassium into cells causes only a minute fractional increase in intracellular potassium though it may reduce extra-

cellular potassium considerably. For example, if half the extracellular potassium in man suddenly shifted into muscle, the concentration of potassium in muscle would increase by only about 1 per cent. Such movement of potassium should lead to hyperpolarization of muscle, for reasons discussed in the preceding paragraph.

However, before we accept the possibility that insulin-induced potassium shifts might hyperpolarize muscle, let us ask why potassium moves into muscle under the influence of insulin. It is generally assumed that it does so because insulin has a primary effect upon glucose uptake. This view, possibly correct, is not yet supported by substantial data and is opposed by observations suggesting independence of potassium uptake from increased glucose uptake due to insulin action.

With these reservations in mind we can re-examine the statements made previously about the relation between membrane potential and ion ratios. The equations can be inverted. If it is true that E_R depends on ion ratios, it is equally true that if by some independent means we can fix E_R and maintain it at its new value, then ions must flow from one side of the membrane to the other until their ratio conforms to that demanded by the new E_R.

These ideas have been explored in part. When insulin is added to a solution bathing rat muscle the membrane potential is increased.[3] In this experiment, in which extracellular potassium concentration is held constant, insulin effect on potassium movement is demonstrated only by an increase in intracellular potassium concentration. The question is which is the horse and which the cart. Serial measurements of potassium concentration in muscle compared to measurements of E_R show that intracellular potassium increases only slowly in the presence of insulin. After three hours' exposure to insulin intracellular potassium is still not as high as predicted by the increase in membrane potential produced in only one hour's exposure to insulin; that is, insulin probably hyperpolarizes muscle before there is appreciable movement of potassium. The degree of hyperpolarization is at least adequate to account for the subsequent movement of potassium. If this is a correct description of the sequence of events, the next question is by what means does insulin produce hyperpolarization. Whatever the intimate details of the answer, the observation hints strongly that insulin acts directly on the muscle membrane. This conclusion, when taken in conjunction with other evidence in the literature, lends added weight to the validity of the transport hypothesis as a prime action of insulin in accelerating glucose metabolism by muscle.

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BOOK REVIEWS

PSYCHOLOGICAL ASPECTS OF AGING. *Edited by John E. Anderson. $2.00, pp. 323, American Psychological Association, Washington, D.C., 1956.*

The "Conference on Planning Research" is one of the current scientific fashions. Whether such conferences succeed in stimulating research is not clear, but occasionally the papers presented at them can be stimulating. This volume represents the proceedings of such a conference on "Planning Research on the Psychological Aspects of Aging." It contains more than a score of papers on personal and social adjustment; on the assessment of aging; on perceptive and intellective abilities; on learning, motivation and education; and on functional efficiency, skills and employment—contributed by social and behavioral scientists from universities throughout the country.

Although the volume contains little that the practitioner can apply directly to the treatment of his patients, and little that the investigator can utilize immediately, it contains a great deal of food for thought. For example, William E. Henry's paper on "Affective Complexity and Role Perceptions," despite its formidable title, considers some very important problems about men and their relation to the world around them. John B. Calhoun's paper on "The Use of Animals in Research on Aging" reminds us again that aging is a phenomenon of all metazoan organisms, and that much can be learned from the laboratory animal. Nancy Bayley and Wayne Dennis have each contributed papers indicating how much can be learned from the longitudinal study of the patient. Ross A. McFarland in his description of the functional efficiency, skills and employment of the aged illustrates how much more precisely one can measure the physiological changes which come with age than the psychological.

Since the management of diabetes is always of long duration, and since a patient with diabetes is most frequently in the older age group, those who concern themselves with the design of therapeutic or investigative procedures to be used with diabetics will do well to study this volume.