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DIE MEGANIEK VAN INSULIEN

Daar is ontsaglik baie oor insulien geskrywe maar ten spyte van alles wat al gedoen is, bly die meganisme, wat hierdie hormoon se werking bepaal, nog 'n raaisel. In onlangse publikasies het Stadie[1, 2] die belangrikheid van verskeie opvattings en hul verwantskap tot mekaar bespreek. Stadie se eie bydrae op hierdie gebied is groot.

Jare gelede al het Minkowski en von Mehring getoon dat 'n toestand wat op suikersiekte gelyk in honde bewerkstellig kan word deur verwydering van die alvleesklier: 'n aanduiding dat die ondoeltreffende metabolisme in suikersiekte te wyte is aan die afwesigheid van een of ander bestanddeel wat deur die pankreas vervaardig word. Later was ontdek dat as die voorste harsingslymklier of die bynier terselfdertyd verwyder word, dit verligting in die toestand bring; daar bestaan dus 'n ingewikkelde tussenspel van die hormone en as die balans versteur word kan dit tot ernstige indien nie noodlottige metabolisme-afwykings lei.

Vir baie jare is die biochemiese beeld van suikersiekte te eenvoudig geteken: 'n ophoping van glukose veroorsaak hiperglisemie en glikosurie, die hoeveelheid glikogeen in spier en lewer neem af, die asemhalingsyfer is laag—te wyte aan verminderde oksidering van glukose —die liggaam verloor vet en weefsel, ketose en verhoogde uitskeiding van stikstof vind plaas. Die gebruik van ligspore in metabolisme-navorsing, die vooruitgang op die gebied van ensiemchemie en die eksperimentele gebruik van oorlewende weefsels help om die insulienmeganiek in intermediêre metabolisme beter te begryp.

Die moontlike biochemiese gebreke, wat deur 'n tekort aan insulien of 'n oormaat van die teengestelde vloeistoffaktore veroorsaak word, kan nou met meer helderheid beskou word. Stadie[1] bespreek die bevindings i.v.m. moontlike insulienmeganiek:

1. Verhoogde deurdringbaarheid van die sel of van die oordrag van glukose in die sel na die plek waar ensiem-aktiwiteit plaasvind.
2. Versnelling van die heksokinase-reaksie.
3. Verhoogde produksie van hoë energie fosfaat en
4. 'n Uitwerking op oksideringsreaksies veral van die Krebs-kringloop.

Die eerste hipotese veronderstel 'n biochemiese gebrek wat 'n ontwrigting veroorsaak in die deurdringing van glukose deur selversperrings tot by die plekke waar ensiem-aktiwiteit plaasvind. By sel-oppervlaktes, of miskien by *cell-particulate interfaces*, wat ensiemstelsels van mekaar skei, bestaan daar versperrings wat

EDITORIAL

THE ACTION OF INSULIN

The literature dealing with insulin is vast; yet in spite of all that has been done the mechanism of action of this hormone remains an unsolved problem. Various concepts have been put forward. The importance of each of these and their relation to one another have been considered in recent publications by Stadie,[1,2] who has himself contributed much in this field.

It is now many years since it was shown by Minkowski and von Mehring that a condition resembling diabetes mellitus can be produced in dogs by removal of the pancreas, indicating that the defective metabolism in diabetes mellitus is due to the absence of some principle produced by the pancreas. It was later found that simultaneous removal of the anterior pituitary or of the adrenal glands ameliorates the condition, showing that there is a complex interplay of hormones whose imbalance may produce serious if not fatal metabolic aberrations.

The biochemical picture in diabetes was for many years greatly over-simplified: accumulation of glucose causes hyperglycaemia and glycosuria, the glycogen in muscle and liver is reduced in quantity, the respiratory quotient is low, owing to diminished oxidation of glucose, and a loss of body fat and body tissue occurs, with ketosis and increased excretion of nitrogen. A better understanding of the action of insulin in intermediary metabolism has been helped by the introduction of tracers into metabolic studies, the development of enzyme chemistry, and the experimental use of surviving tissues.

The possible biochemical defects caused by deficiency of insulin or excess of the opposing humoral factors can now be considered more intelligibly. Stadie[1] has evaluated the evidence for the possible modes and sites of action of insulin. These are (1) an increase of cell permeability or transfer of glucose across the cell to sites of enzyme activity, (2) acceleration of the hexokinase reaction, (3) increase of high-energy phosphate formation, and (4) an effect on oxidative reactions, particularly of the Krebs cycle.

In the first hypothesis there is believed to be a biochemical lesion which disturbs the permeation of glucose across cell barriers to sites of enzyme action. At cell surfaces, or perhaps at cell-particulate interfaces which separate enzyme systems from one another, there

miskien verstoor word wanneer die balans van hormone soos bv. insulien omver gegooi word. Daar is rede om te glo dat hormone invloed uitoefen op die oordrag van glukose en anders suikers na die ensiemvestings. Die versperring wat glukose agter selgrense hou word deur die werking van insulien gelig, maar hoe hierdie meganisme werk is nog onbekend.

Die tweede biochemiese gebrek, wat moontlik op 'n tekort aan insulien volg, staan in verband met glukose-aktivering. Normaal word glukose vir verdere stofverwisseling voorberei deur die vorming van glukose-6-fosfaat gekataliseer deur gluko-heksokinase wat in feitlik alle selle gevind word. As die werking van hierdie ensiem gesteur word, word minder glukose-6-fosfaat saamgestel. Hierdie belemmering in die heksokinase-reaksie kan miskien al die metaboliese steurings verklaar wat by suikersiekte bespeur word. Dit kom egte voor of die bewyse i.v.m. met eersgenoemde hipotese—waarby 'n oordra-meganisme betrokke is—meer oortuigend is as dié ten gunste van 'n reaksie op heksokinase of ander spesifieke ensieme.

Ten derde bestaan daar baie bewyse om die opvatting te staaf dat gebrekkige produksie van hoë energie fosfate in verband staan met suikersiekte of insulienmeganiek. Indirekte bewyse dui aan dat hoë energie fosfaat wel onder suikersiekte-toestande vervaardig word. Meer direkte bewyse is verkry met die studie van protoplasmadrade deur middel van die differensiële sentrifugering van lewerhomogenate. Sulke tegnieke bewys dat gebrekkige oksidatiewe fosforilering plaasvind in die lewer (protoplasmadraadbereidings) van katte wat se alvleesklier verwyder is. Die juiste betekenis van hierdie bevindings vereis verdere navorsing.

'n Vierde moontlike plek waar insulienwerking plaasvind, word in die literatuur bespreek. Dit staan in verband met oksideringsreaksies waarby die Krebs-kringloop betrokke is, maar omdat afwykende resultate met sekere eksperimente verkry is,[1] word die bestaan van hierdie suikersiektegebrek nie geheel en al aanvaar nie.

Op hierdie stadium kan geen grondige uitspraak oor die insulienmeganiek gegee word nie.

1. Stadie, W. C. (1955): Amer. J. Med., **19,** 257.
2. *Ibid.* (1954): Phys. Rev., **34,** 52.

are barriers that may be altered by imbalance of hormones such as insulin. There is evidence that the transfer of glucose and other sugars to enzyme sites is under hormonal control. The barrier which can prevent glucose from passing across cell boundaries is lifted by the action of insulin, but the mechanism of action remains unknown.

The second biochemical lesion which may possibly occur when there is lack of insulin is related to the activation of glucose. Glucose is normally prepared for further metabolism by the formation of glucose-6-phosphate catalyzed by glucohexokinase which is present in practically all cells. Interference with the action of this enzyme results in diminished formation of glucose-6-phosphate. This impairment of the hexokinase reaction might explain all the metabolic derangements observed in diabetes mellitus. However, the evidence for the first-mentioned hypothesis, involving a 'transfer mechanism' appears to be stronger than that in favour of an action on hexokinase or other specific enzymes.

Thirdly, there is much evidence to support the view that defective production of high-energy phosphates is associated with the diabetic state or the action of insulin. Evidence of indirect nature has indicated that high-energy phosphate formation does occur in the diabetic state. More direct evidence has been obtained from a study of mitochondria obtained by differential centrifugation of homogenates of liver. By such techniques oxidative phosphorylation was found to be deficient in the liver (mitochondrial preparations) of depancreatized cats. The full significance of these findings requires further study.

A fourth possible site of action of insulin considered in the literature is concerned with the oxidative reactions involving the Krebs cycle, but because of anomalous results obtained in certain experimental studies,[1] the existence of this type of diabetic defect has not been altogether convincing.

No decision can be made at this stage concerning the true mode of action of insulin.

1. Stadie, W. C. (1955): Amer. J. Med., **19,** 257.
2. *Ibid.* (1954): Phys. Rev., **34,** 52.