The fact that one of the major actions of insulin on muscle is to stimulate passage of glucose across the membrane makes it unlikely that effects of the hormone are to be seen in cell-free systems, and indeed few observations of this sort have been reported. Likewise, if the stimulation by insulin of incorporation of amino acids into protein arises from an action of the hormone to regulate the intracellular distribution and availability of ATP we should again expect the capacity of a tissue to respond to insulin to be lost on homogenisation. If, on the other hand, the effect of insulin on amino acid incorporation were to result from a direct interaction of the hormone with the protein synthesizing system, such an effect might still be seen in a cell-free system. It was thus thought of interest to seek to establish whether insulin could influence amino acid incorporation in homogenates or under conditions in which the membrane characteristics of muscle were varied by changes in the ion content of the supporting buffer. In general the effect of insulin is not seen in these broken cell preparations, from which observations conclusions as indicated above can be drawn. However, a number of behavioural characteristics of the incorporating system lead to the belief that the optimal conditions for protein synthesis in cell-free preparations have yet to be discovered and an effect of insulin in these circumstances may be dependent on satisfying a number of conditions as yet inadequately determined. It is hoped to discuss observations bearing on these problems.

2. Some relationships between cation transport, carbohydrate metabolism and insulin action in muscle.

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Isolated rat and mouse hemidiaphragms were incubated in Krebs-Ringer bicarbonate buffer. The active transport of Na⁺ and K⁺ across cell membranes is known to be decreased in potassium-free media. Lowering of the K⁺-concentration from 6 to 0 mM/L was shown to cause up to 200% stimulation of ¹⁴C-glycogen synthesis in the diaphragm. This insulin-like effect was not paralleled by an increased glucose uptake. However, the increased glycogen synthesis was followed by a decreased lactate production. Ouabain (g-strophantine), which is a potent inhibitor of active cation transport was shown at normal K⁺-concentration to produce essentially the same effects when added to the incubation medium. Changes in the sodium concentration of the incubation medium had the following effects: the glucose uptake and lactate acid production were stimulated at concentrations of sodium higher than normal, and inhibited at concentrations lower than normal; the stimulation of glucose uptake by insulin (0.1 i. u./ml) was most pronounced at 143 mmol of sodium, being diminished both at the higher and the lower concentration of sodium; the stimulatory effect of insulin upon glycogen synthesis and lactate production was correspondingly diminished at high and low concentrations of sodium.

It is suggested that the cation transport plays a central role in the regulation of carbohydrate metabolism and the action of insulin thereon.

3. Inhibition of the action hypoglycaemiantes de l’insuline par des solutions d’acides aminés.


L’insuline, additionnée d’une quantité traceuse d’insuline-¹³¹ et d’arginine en concentrations croissantes (de 1 à 50 mg/ml) est chromatographiée dans le système butanol-acide acétique-eau. On obtient 2 pics de radio-activité; l’un au départ, l’autre migrant avec le front de l’arginine. Il existe une relation trés nette entre l’importance du deuxième pic et la concentration d’arginine dans le mélange.


tionsmöglichkeiten auf 2 einzuüberschränken. Die einzelnen Präparate wurden bezüglich ihrer Fähigkeit, am isolierten Rattenfettgewebe die $^{14}CO_2$-Produktion aus $^{14}C$-Glucose und die Glucoseaufnahme am isolierten Rattennierenlappen zu beeinflussen, untersucht. Während natürliche und synthetische A- und B-Ketten allein, sowohl A-Insulin-Präparationen aus 2 A-Ketten wie A-Insulin-Präparationen aus A- und B-Ketten die $^{14}CO_2$-Produktion und die Glucoseaufnahme der isolierten Gewebe zu stimulieren, die Aktivität der Insuline aus synthetischen und natürlichen A- und B-Ketten beträgt ohne Voroxydation der A-Kette 1 bis 2%. Erfolg die Kombination der beiden Ketten nach Vorbildung der Disulfidbrücke der A-Kette (Voroxydation), so beträgt die biologische Aktivität der Insulinpräparationen aus natürlichen A- und B-Ketten bis zu 30%. Das Molekulargewicht der Kombinationspräparate liegt etwa bei 60 000. Die biologische Aktivität am Rattenfettgewebe und am Rattendiaphragma ist durch Insulinanimitkörper vollständig hemmbar.

5. Attempts to discover if the brain is insulin sensitive in vivo in man.


There is controversy about the insulin sensitivity of the CNS, but clinicians are familiar with the paradox of diabetics who are comatose from insulin hypoglycaemia at blood sugar levels higher than at which they are conscious on other occasions. Other studies on the peripheral tissues in man have shown that there is a glucose threshold that must be exceeded by the arterial glucose level before a shift can occur from the vascular bed and which is sensitive to insulin [Butterfield, W. J. H., E. H. Holling: Clin. Sci. 18, 147 (1959); Butterfield W. J. H., and M. J. Whitchello; Diabetes 11, 251 (1962)]. Experiments were performed in 4 fasting subjects to discover if there was a similar threshold in the brain and determine if it was affected by 0.1 u insulin i.v. Estimations of NEFA (DOLE), insulin (HALES and RANDLE) glucose (HOFFMAN) and free amino acid levels (MOORE and STREIN) were made in blood from catheters inserted into the jugular bulb, the brachial artery and a vein draining the deep forearm muscles. Forearm blood flow was measured with a plethysmograph and cerebral blood flow by the Kety Schmidt or the external counting technique of Veall and Mallet using radio-active Xenon. The results confirm a peripheral tissue glucose threshold and suggest that there is a tissue glucose threshold in the brain which is also sensitive to insulin, but which responds more slowly than the peripheral tissues. NEFA levels were not remarkable. The alarm response of the CNS to hypoglycaemia, probably related to the decrease in available glucose, is reflected by the forearm blood flow. The cerebral exchange of amino acids indicates an uptake of certain acids; others were apparently released.


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Forearm glucose metabolism was studied in 25 patients, non-diabetics and diabetics, by means of a technique based upon simultaneous measurements of forearm blood flow and arteriovenous true glucose difference. Glucose, phosphorus and potassium uptakes by muscle both the fasting and resting conditions were calculated using Fick's principle. Forearm blood flow was determined by venous occlusion plethysmography and "true blood sugar" by the glucose oxidase method on samples obtained from deep veins draining only muscles.

It was shown that: 1. the glucose uptake by forearm muscle in fasting normal controls was $+0.70 \mu mol/\text{min} /100 \text{ml}$ (Sm $\pm 0.19$) in severe diabetics, $-0.47 \mu mol/\text{min} /100 \text{ml}$ (Sm $\pm 0.47$) in and in mild diabetics $+0.05 \mu mol/\text{min} /100 \text{ml}$; 2. there was a statistically significant positive correlation between arterial blood sugar and forearm glucose uptake; 3. injection of glucagon-free insulin into the brachial artery increased variably the forearm glucose uptake without affecting systemic blood sugar; 4. forearm phosphorus uptake was $+0.09 \mu mol/\text{min} /100 \text{ml}$ in normals and $+0.05 \mu mol/\text{min} /100 \text{ml}$ in diabetics; 5. forearm potassium uptake was $-0.08 \mu mol/\text{min} /100 \text{ml}$ in normals and $-0.34 \mu mol/\text{min} /100 \text{ml}$ in diabetics; 6. there was a statistically significant relationship between plasma glucose and forearm uptakes both in normal and diabetic subjects; 7. on the other hand, no correlation was found between potassium and glucose forearm uptakes.

7. Intestinal factors and insulin secretion.


Slow infusion of glucose into the jejunum of normal subjects led to a smaller rise of blood glucose than administration of the same amount of glucose intravenously. Nevertheless plasma insulin levels were higher following intrajejunual glucose than after intravenous glucose despite the lower blood sugar levels. More rapid administration of glucose enhanced this inverse relationship between blood glucose and plasma insulin levels. Observations were also made on two subjects who had had end-to-side portacaval shunts and similar results were obtained. The most likely explanation for these results seemed to be that a humoral substance was released from the intestinal wall which stimulated insulin release by the pancreatic beta cells.

8. Relationships between calcium-phosphorus homeostasis in alloxan diabetic rats and parathyroid morphology in their offspring.


Previous investigations have shown that the parathyroid glands in newborns of diabetic mothers are larger than those of normal ones. Children of diabetic mothers sometimes show impaired calcium-phosphorus homeostasis with tetany during the first days of extrauterine life. In a study of serum calcium and phosphorus in pregnant alloxan diabetic rate and of the parathyroids of their offspring, we have found that the parathyroid enlargement is significantly correlated to the altered calcium-phosphorus homeostasis in the mothers. Such altered calcium-phosphorus homeostasis can be a tentative explanation of the tetany in newborn infants of diabetic mothers.

9. Etude de la cinétique du glucose au moyen de perfusions continues de glucose, glucose + cortisol, insulin.


Un modèle du système à feedback négatif à deux compartiments (glucose et insuline) interprète de façon satisfaisante l'effet de la perfusion continue de glucose intraveineux chez des sujets normaux et chez des diabétiques. Chez les sujets normaux le pouvoir régulateur du système ramène la glycémie, au cours de la perfusion, à des valeurs proches des valeurs de départ. La