The Lancet · Saturday 13 April 1963

THE GLUCOSE FATTY-ACID CYCLE
ITS ROLE IN INSULIN SENSITIVITY AND THE METABOLIC DISTURBANCES OF DIABETES MELLITUS *

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SEVERAL abnormalities of carbohydrate metabolism, common to many endocrine and nutritional disorders, are associated with a high plasma concentration of non-esterified fatty acids (N.E.F.A.). These abnormalities include impaired sensitivity to insulin; impaired pyruvate oxidation; emphasis in muscle on conversion of glucose to glycogen rather than to pyruvate; and, frequently, impaired glucose tolerance. The endocrine and nutritional disorders include diabetes, starvation, carbohydrate deprivation, excess of growth hormone and corticosteroids in acromegaly or Cushing's syndrome or following administration of the hormones, and perhaps obesity. We now wish to summarise evidence which appears to show that the high plasma concentration of N.E.F.A. (or the underlying breakdown of glycerides of which it is a symptom) stands in a causal relationship to these abnormalities of carbohydrate metabolism, and we suggest that this is a distinct biochemical syndrome which could appropriately be called the fatty-acid syndrome. We wish to propose further that there are interactions between glucose and fatty-acid metabolism in muscle and adipose tissue which take the form of a cycle (the glucose fatty-acid cycle), and which are fundamental to the control of glucose and fatty-acid concentrations in the blood, and of insulin sensitivity.

The Glucose Fatty-acid Cycle

The concept of a glucose fatty-acid cycle is shown in diagrammatic form in figs. 1 and 2. The essential features are (1) the restrictions imposed on glucose metabolism in muscle by the release for oxidation of more fatty acids derived from muscle or adipose-tissue glycerides, and (2) those imposed on release of fatty acids from glycerides by uptake of glucose. In the tissue phase, fatty acids and glycerol are released from glycerides in both muscle and adipose tissue (lipolysis): they may be reincorporated into glycerides by esterification with glycerolphosphate formed from glucose, but not by reaction with glycerol, which is released into extracellular fluid. Fatty acids may also be oxidised (both tissues), or transferred to plasma albumin (adipose tissue). In the blood phase, uptake of glucose by adipose tissue is depicted as inhibiting the flow of fatty acids from adipose tissue (and of ketone bodies formed from them in the liver) to muscle through the blood-stream; and the increased availability, for oxidation, of fatty acids (from muscle or adipose-tissue glycerides) or of ketone bodies is depicted as inhibiting glucose uptake by muscle. The cycle thus provides a primitive mechanism which, quite independently of hormonal control, will tend to maintain a constant plasma-glucose concentration in animals that feed intermittently. Control by the cycle is modified by insulin, which enhances glucose uptake in muscle and adipose tissue, inhibits release of fatty acids in adipose tissue, and increases esterification of fatty acids in adipose tissue and muscle. It may be noted that the effects of the hormone on glyceride metabolism may potentiate its effects on glucose uptake. Growth hormone, corticosteroids, and adrenaline, on the other hand, modify control by the cycle by accelerating release of fatty acids from adipose-tissue and muscle glycerides, and may through this action inhibit uptake of glucose by muscle at a particular insulin concentration—i.e., induce insulin insensitivity.

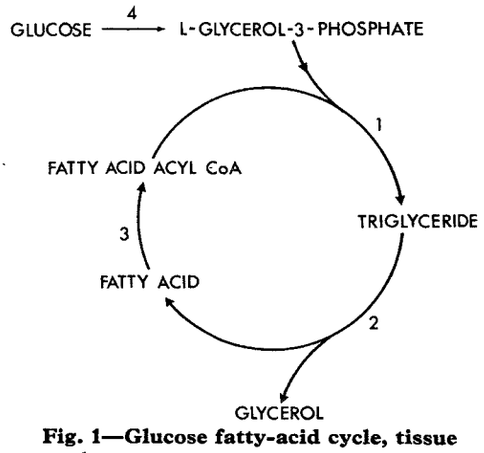

Fig. 1—Glucose fatty-acid cycle, tissue phase.
1. Esterification.
2. Lipolysis.
3. Fatty-acid activation.
4. Glycerol phosphate synthesis.

Experimental Evidence

The experimental evidence for a glucose fatty-acid cycle is derived from two lines of investigation. Firstly, evidence for changes in the rate of release of fatty acids in different clinical and experimental conditions; and, secondly, evidence that fatty acids and ketone bodies can induce changes in carbohydrate metabolism in muscles of normal animals similar to those seen in muscle in diabetes and related disorders.

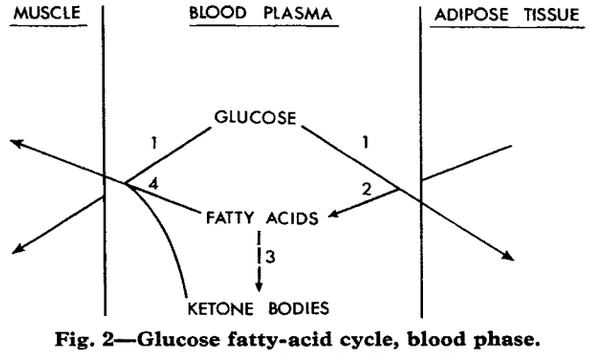

Fig. 2—Glucose fatty-acid cycle, blood phase.
1. Uptake of glucose by muscle and adipose tissue.
2. Release of fatty acids from adipose tissue to plasma albumin.
3. Formation of ketone bodies from fatty acids by liver.
4. Uptake of fatty acids and ketone bodies by muscle.

* Based in part on postgraduate lectures given by one of us (P. J. R.) at Queen's College, Dundee, and the Middlesex Hospital, London, in January and November, 1962.

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TABLE I—GLYCEROL OUTPUT BY RAT HEART, DIAPHRAGM, AND EPIDIDYMAL FAT-PAD

Experiment	Insulin (units × 10^{-3} per ml.)	Glycerol output (μ-moles per g. per hr.)		
		Heart	Diaphragm	Epididymal fat-pad
Control	..	1·77 ± 0·15	0·49 ± 0·07	0·66 ± 0·60
Starved 48 hr.	..	2·58 ± 0·17	0·64 ± 0·06	1·30 ± 0·19
Alloxan diabetic	..	4·10 ± 0·53	0·81 ± 0·04	1·15 ± 0·10
Control	100	2·66 ± 0·21	0·66 ± 0·09	0·87 ± 0·05
Starved	100	3·81 ± 0·27	0·72 ± 0·09	1·27 ± 0·15
Alloxan diabetic	100	4·62 ± 0·22	1·15 ± 0·12	1·26 ± 0·03
Hypophysectomised	100	1·46 ± 0·07	0·45 ± 0·04	0·45 ± 0·04
Hypophysectomised diabetic	100	1·17 ± 0·05	0·53 ± 0·03	0·58 ± 0·03
Hypophysectomised diabetic treated with growth hormone and cortisol	100	..	0·86 ± 0·12	1·67 ± 0·37
Control	..	..	0·52 ± 0·04	..
Adrenaline (20 μg. per ml.)	..	..	1·24 ± 0·08	..
Growth hormone (100 μg. per ml.)	100	..	1·14 ± 0·17	..
Control	100	..	0·64 ± 0·07	..
Control	..	..	0·47 ± 0·03	0·81 ± 0·06
Insulin	100	..	0·47 ± 0·03	0·58 ± 0·05

Glucose concentration: hearts 1 mg. per ml., diaphragms and fat-pads 1·5 mg. per ml.
Glycerol assayed by method of Garland and Randle (1962).

Fatty-acid Release

The release of fatty acids from adipose tissue has been investigated by measuring plasma concentrations of N.E.F.A. in man and laboratory animals, and by estimation of fatty-acids transferred to plasma albumin by rat adipose tissue in vitro. These studies have shown that release of fatty acids is diminished by glucose, insulin, and panhypopituitarism, and enhanced by diabetes (clinical and experimental), starvation, carbohydrate deprivation, and actions of growth hormone, corticosteroids, and adrenaline (White and Engel 1958, Gordon and Cherkes 1958, Jeanrenaud and Renold 1960, Dole 1956, Gordon and Cherkes 1956, Bierman et al. 1957, Raben and Hollenberg 1960, Hales and Randle 1963). Since isolated rat diaphragm and perfused rat heart muscle cannot metabolise glycerol, use has been made of the suggestion of Vaughan (1961) that glycerol output may be used as an index of the rate of glyceride breakdown in tissues in which it is not metabolised. With this method evidence has been obtained that glyceride breakdown in rat diaphragm and rat heart muscle in vitro is enhanced by alloxan diabetes, starvation, treatment of the rat with growth hormone and cortisol, and by treatment of the isolated muscle with growth hormone and adrenaline. Glyceride breakdown is diminished in hypophysectomised or alloxan-diabetic hypophysectomised rats. Insulin in vitro diminished output of glycerol by adipose tissue, but not by diaphragm or heart muscle (table I) (cf. Jungas and Ball 1962). Further evidence has been obtained, in preliminary experiments, that the intracellular concentration of fatty acids in diaphragm is increased 50% by starvation and 100% by alloxan diabetes.

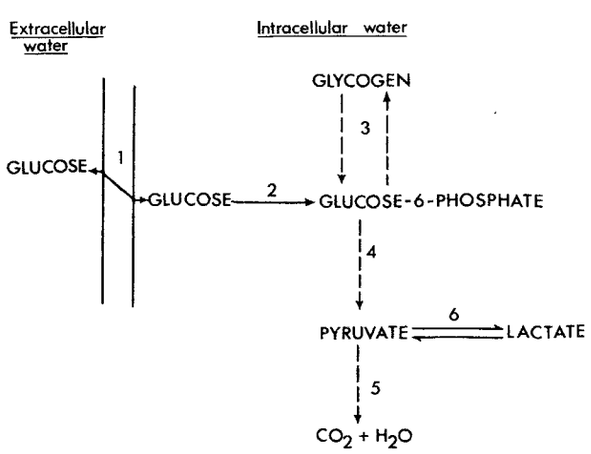

Fig. 3—Glucose metabolism in muscle.

1. Membrane transport of glucose.
2. Phosphorylation of glucose.
3. The glycogen cycle.
4. Glycolysis.
5. Pyruvate oxidation.
6. Lactate dehydrogenase reaction.

Effects of Fatty Acids and Ketone Bodies

Glucose metabolism in muscle.—Fig. 3 summarises, in a simplified form, details of glucose metabolism.

Glucose uptake from the extracellular compartment involves, first transfer of glucose across the cell membrane (membrane transport), and then conversion of glucose to glucose 6-phosphate within the cell by an irreversible reaction catalysed by the enzyme hexokinase (phosphorylation of glucose). Either step may limit uptake of glucose by muscle, and it is possible to ascertain which is limiting by measuring the intracellular glucose concentration. This increases when phosphorylation of glucose limits its uptake and falls when membrane transport is limiting. Membrane transport may also be separately investigated by studying the rate of transfer of analogues of glucose (e.g., L-arabinose), which are not phosphorylated. Transfer of glucose is specifically accelerated by insulin, but glucose phosphorylation is little affected by the hormone. Insulin insensitivity may thus be due to diminished responsiveness of the membrane-transport system to the action of the hormone, or to inhibition of glucose phosphorylation.

Glucose 6-phosphate may either be converted to or formed from glycogen by the glycogen cycle (two independent pathways catalysed by different enzymes leading to glycogen synthesis and breakdown), or broken down to pyruvic acid by glycolysis (essentially irreversible in muscle). Pyruvate once formed may be lost from the cell, either unchanged or as lactate (formed by reduction with $NADH_2$—reduced coenzyme I). The proportions of lactate and pyruvate lost from the cell appear to depend upon the proportions of oxidised and reduced coenzyme I within the cell. It is interesting to note that pyruvate and lactate are the only major products of glucose metabolism (other than carbon dioxide) which leave the cell, and that they can be reconverted to glucose in the liver. Finally, pyruvate may be oxidised to carbon dioxide and water by pyruvate dehydrogenase and enzymes of the citrate cycle.

The rate of pyruvate oxidation can most readily be ascertained by measuring pyruvate uptake by isolated tissues or by measurement of pyruvate tolerance in living animals, with correction for that portion of the pyruvate taken up which is converted to lactate. Less satisfactory evidence can be obtained by a study of pyruvate and lactate formation from glucose. Changes in pyruvate output by isolated tissues, or in blood-pyruvate concentrations in animals, are themselves of little value in drawing conclusions about changes in pyruvate oxidation.

TABLE II—EFFECT OF DIABETES, AND OF FATTY ACIDS AND KETONE BODIES ADDED IN VITRO, ON CARBOHYDRATE METABOLISM OF RAT HEART AND RAT DIAPHRAGM MUSCLES

Experiment	Insulin (units × 10^{-3} per ml.)	Glucose uptake (mg. per g. wet muscle per hr.)	Intracellular glucose concentration (mg. per 100 ml.)	Glucose 6-phosphate (μ-moles per 100 g.)	Glycogen: difference from control (mg. per g. per hr.)	Lactate + pyruvate output (mg. per g. per hr.)
Heart:						
Control ± 2% bovine plasma albumin ..	100	10·8 to 14·2 ± 0·70	11 ± 3 to 18 ± 6	29 ± 0·8	..	3·9 to 4·9
β-hydroxybutyrate (70 mg. per 100 ml.) ..	100	5·0 ± 0·60	46 ± 6	56 ± 1·4	3·4 ± 1	..
Albumin + palmitate (0·75 mM)	100	7·7 ± 0·70	46 ± 3·4	39 ± 1·1	1·0 ± 1	4·3
Control ± 2% bovine plasma albumin ..	..	8·6 to 9·2 ± 0·72	0 to 11 ± 3	21 ± 2·5	..	..
β-hydroxybutyrate (70 mg. per 100 ml.) ..	..	2·6 ± 0·7	16 ± 3·8	41 ± 4·3	..	..
Albumin + palmitate (0·75 mM)	..	4·4 ± 0·28	6 ± 1	30 ± 2·5	..	..
Alloxan-diabetes	100	5·8 ± 0·60	32 ± 6	46 ± 5·6	..	4·7
Diaphragm:						
Control	100	6·8 ± 0·17	..	..	..	1·83 ± 0·06
Butyrate (25 mg. per 100 ml.)	100	6·2 ± 0·20	..	..	0·25 ± 0·22	1·60 ± 0·06
0·85% albumin control	1	4·25 ± 0·16	..	..	..	0·99 ± 0·06
Albumin + palmitate (0·6 mM)	1	3·65 ± 0·16	..	..	0·10 ± 0·33	0·94 ± 0·05
Control	100	4·9 ± 0·34	..	..	..	1·20 ± 0·08
Alloxan-diabetes	100	4·3 ± 0·30	..	..	0·10 ± 0·21	1·29 ± 0·02

Glucose concentration 1 mg. per ml. for hearts, 1·5 mg. per ml. for diaphragms. With perfused hearts acetoacetate (25 mg. per 100 ml.) had quantitatively similar effects to β-hydroxybutyrate; and butyrate (30 mg. per 100 ml.), octanoate (70 mg. per 100 ml.) without albumin, and oleate (mM) carried by 2% albumin, had effects similar to those of palmitate; the effects of starvation were similar to, but smaller than, those of diabetes.

because of the possibility that they may be due to alterations in the ratio of lactate to pyruvate in blood or incubation medium. Information about relative rates of glycogen synthesis and breakdown can be obtained by estimating the glycogen concentration in the tissue, whereas the rate of metabolism of glucose 6-phosphate by glycolysis can be calculated approximately as that portion of glucose taken up which is not converted to glycogen. Further information can be obtained by measuring the glucose 6-phosphate concentration in the cell, because this may be increased when glycolysis is impaired.

Glucose uptake and insulin sensitivity in muscle.—The action of insulin on uptake of glucose by muscle in vivo, and by isolated rat diaphragm and perfused rat heart muscle in vitro, is known to be impaired by diabetes, starvation, and treatment of the rat with growth hormone or cortisol, and by in-vitro addition of adrenaline (and inconsistently by preparations of growth hormone); and enhanced by hypophysectomy or adrenalectomy (Manchester, Randle, and Young, 1959, Kipnis 1959, Morgan, Henderson et al. 1959, Newsholme and Randle 1961, Groen et al. 1958, Ottaway and Bulbrook 1955, Park et al. 1961). There is evidence, based upon measurements of insulin-glucose tolerance and of arteriovenous glucose differences in limbs, that in man uptake of glucose by muscle in the presence of insulin is impaired in diabetes, in acromegaly, and after dietary restriction of carbohydrate (Himsworth 1939, Butterfield 1961). In-vivo studies in the rat, and in-vitro studies with rat heart and rat diaphragm, have shown that diabetes and diabetogenic hormones reduce sensitivity to insulin in muscle by impairing phosphorylation of glucose and diminishing the activating action of insulin on membrane transport of glucose (Kipnis 1959, Park et al. 1961, Newsholme and Randle 1961, Riddick et al. 1962). There are thus two steps in carbohydrate metabolism involved in impairment of insulin action on muscle cells. These changes in diabetic or starved rats can be reversed by hypophysectomy, adrenalectomy, or treatment of the diabetic rat with insulin.

Table II shows, in hearts from normal, starved, and diabetic rats, the changes in glucose uptake induced by long-chain fatty acids carried by plasma albumin, short-chain fatty acids, and ketone bodies. In the presence of insulin at a high concentration (0·1 unit per ml.) fatty acids and ketone bodies reduced glucose uptake in hearts from normal rats to levels comparable to those seen in tissues from diabetic or starved animals (see also Williamson and Krebs 1961). Fatty acids and ketone bodies, like diabetes and starvation, led to substantial intracellular accumulation of glucose, showing that phosphorylation of glucose was impaired. When hearts from fed normal rats (plasma-insulin concentration more than 130 microunits per ml.) were perfused with medium lacking insulin, glucose uptake was similar to that seen in experiments in which the medium contained insulin at a high concentration. It seems reasonable, therefore, to suggest that these hearts were subject to the influence of a physiological amount of insulin carried over in the tissue when it was removed from the animal. Under these conditions addition of fatty acids or ketone bodies led to a very marked inhibition of glucose uptake which was associated with only slight intracellular accumulation of glucose (see also Shipp et al. 1961). The tentative conclusion is drawn that fatty acids and ketone bodies had almost totally suppressed the influence on glucose transport of insulin in the heart. Some further evidence for this view has been provided by the observation that fatty acids and ketone bodies can impair the transfer of the glucose analogue L-arabinose in rat heart.

In diaphragm muscle from normal rats, palmitate (carried by plasma albumin) and butyrate depressed uptake of glucose in the presence of insulin, and the degree of impairment was similar to that seen in diabetes.

Glycogen metabolism.—That the concentration of glycogen in the heart is increased in diabetes and starvation has long been known (Cruickshank 1913, McLeod and Prendergast 1921). Moreover, treatment of fasting hypophysectomised or normal rats with growth hormone increases cardiac glycogen, and feeding hypophysectomised rats with long- or short-chain fatty acids or high-fat diets can increase glycogen in heart and skeletal muscle (Russell and Wilhelmi 1950, Lackey et al. 1946, Bowman 1959, Samuels et al. 1942). In hearts from normal rats perfused in vitro, ketone bodies (and to a lesser extent fatty acids) added to the perfused medium increased cardiac glycogen even though uptake of glucose was diminished (table II). In rat diaphragm muscle the rate of glycogen synthesis was maintained even though glucose uptake was diminished by in-vitro addition of fatty acids or the development of alloxan diabetes (table II).

Glycolysis.—The rate of glycolysis is markedly reduced in perfused isolated rat heart by diabetes and starvation, and in normal hearts by addition of fatty acids and ketone bodies to the perfused medium. Inhibition of glycolysis is associated in each instance with intracellular accumulation of glucose 6-phosphate (table II). Newsholme and Randle

(1962) suggest that this inhibition of glycolysis and the enhanced deposition of glycogen in these conditions results from inhibition of the phosphofructokinase reaction in rat heart. In rat diaphragm muscle glycolysis was impaired equally by diabetes and by in-vitro addition of fatty acids (table II).

Pyruvate metabolism.—In normal people pyruvate tolerance is known to be impaired by treatment with prednisone (Fajans 1961), and in dogs growth hormone exerts a similar effect (Weil et al. 1961). In patients with Cushing's syndrome, or people treated with corticosteroids, plasma concentrations of pyruvate and lactate are raised, which suggests that pyruvate oxidation is impaired (Henneman and Bunker 1957). There is no comparable evidence for impairment of pyruvate oxidation in human diabetes, though the plasma concentration of pyruvate is increased during insulin-glucose tolerance tests in human diabetic patients (Fry and Butterfield 1962). Since Klein (1942) had previously shown that the ratio of lactate to pyruvate in blood plasma is not changed in man by diabetes or by glucose or insulin, the findings of Fry and Butterfield could be accepted as evidence for impaired pyruvate oxidation. In rat heart or rat diaphragm muscle the oxidation of pyruvate (added to the perfusion or incubation medium, or formed in the tissue from glucose) was impaired about equally by diabetes, starvation, and (in experiments with tissues from normal animals) by the in-vitro addition of fatty acids and ketone bodies (Garland, Newsholme, and Randle 1962). Similar effects of fatty acids on pyruvate oxidation in vitro have also been noted in liver and kidney slices.

Effect of anoxia and hypoglycæmic substances.—Further evidence that release of more fatty acids or ketone bodies for oxidation is responsible for diminished phosphorylation of glucose and impaired glycolysis in muscle has accrued from studies of the effects of anoxia and sodium salicylate. These agents completely abolish the inhibitory effects of diabetes, and of fatty acids and ketone bodies, on these steps in carbohydrate metabolism. This effect of salicylate could be an important factor in its known hypoglycæmic action in human diabetics. The observation that another hypoglycæmic compound, hypoglycin, is an inhibitor of fatty-acid oxidation might also support the view that this process is intimately concerned with the control of glucose metabolism in muscle (McKerns et al. 1960).

Fatty Acids, Diabetes, and Insulin Sensitivity

Fatty Acids and Insulin Sensitivity

The experimental evidence which has been summarised appears to establish that abnormalities of glucose phosphorylation, glycogen metabolism, glycolysis, and pyruvate oxidation in muscles of diabetic or starved animals, or of animals treated with growth hormone and corticosteroids, are secondary to the release of more fatty acids or ketone bodies for oxidation. It suggests, moreover, that impaired oxidation of pyruvate in human diabetes, in Cushing's syndrome, and in people treated with corticosteroids is due to this excess of fatty acids; that impaired oxidation of pyruvate should be found in acromegalic patients with a high plasma concentration of N.E.F.A.; and that the other abnormalities of carbohydrate metabolism in muscles of laboratory animals which have been attributed to a higher rate of release of fatty acids may also occur in human muscle in these disorders. Greater availability of fatty acids is likely to be an important factor in the insensitivity to insulin seen in muscles from diabetic animals, or from animals treated with growth hormone and corticosteroids. The insulin antagonism induced by adrenaline in vivo or in muscle in vitro may well be secondary to the release of fatty acid induced by the hormone, and not, as has been suggested, to breakdown of glycogen.

The question as to whether an alteration in the rate of release of fatty acids is the only factor involved in changes in insulin sensitivity in muscle cannot be answered at the present time. Certainly the rate of glyceride breakdown in adipose tissue and muscle is invariably increased in conditions associated with diminished insulin sensitivity and vice versa. The possibility remains, however, that changes in the sensitivity of the membrane transport system for glucose to the influence of insulin might involve additional actions of growth hormone or corticosteroids which are not connected with their influence on glyceride breakdown.

The experimental evidence discussed above has been restricted to a consideration of effects of fatty acids derived from glycerides of muscle or transported from adipose tissue as plasma N.E.F.A. on glucose metabolism in muscle. There is also the possibility that other serum lipid fractions (e.g., glycerides or lipoproteins) might influence glucose metabolism in muscle through the provision of fatty acids. In this connection Stewart (1941) has observed that the intravenous injection of a fat emulsion into a normal rabbit could produce almost complete insensitivity to the hypoglycæmic action of a test dose of insulin.

Fatty Acids and Human Diabetes

Our suggestion that release of more fatty acids for oxidation in muscle may be an important cause of insulin insensitivity, can provide a reasonable explanation for many hitherto unexplained features of human diabetes. Early diabetics are frequently obese, and the development of hypoglycæmia some hours after food is well documented. Moreover, insulin-glucose tolerance tests have shown that insensitivity to insulin action in diabetes (or carbohydrate deprivation) takes the form of a delayed response to the hormone (Himsworth 1939). At first sight obesity (the retention of glyceride) might appear to be incompatible with the view that an enhanced rate of glyceride breakdown is responsible for insensitivity to insulin, particularly since fatty-acid synthesis in adipose tissue is generally impaired when glyceride breakdown is accelerated. The paradox may be explained if in humans as in the rat, insulin inhibits glyceride breakdown in adipose tissue but not in muscle (cf. table I). The sequence of events in early diabetes might then be as follows. In the fasting state, in spite of a normal or raised plasma concentration of insulin, the rate of glyceride breakdown in muscle and adispose tissue is increased. After intake of food or glucose the plasma concentration of insulin rises higher, lipolysis is inhibited in adipose tissue but not in muscle, and the plasma concentration of N.E.F.A. falls (Hales and Randle 1963). Uptake of glucose by adipose tissue, and synthesis of fatty acids and deposition of glycerides in the tissue then take place at an abnormally high rate because of the continuing high concentrations of insulin and glucose. Muscle glycerides, on the other hand, continue to be broken down at a rate which exceeds esterification of fatty acid, and insensitivity to insulin and diminished glucose uptake persist in this tissue. Eventually, when the plasma concentration of N.E.F.A. falls to a normal level, muscle may be able to

re-esterify fatty acid quickly enough for its intracellular concentration to fall towards normal, and for glucose uptake to increase. At this stage, and with the persistence of a high concentration of insulin, the plasma-glucose concentration might fall precipitously and hypoglycæmia develop.

Fatty Acids and Albumin Antagonism to Insulin

In plasma from diabetic animals several factors have been detected which are capable of antagonising the action of insulin on uptake of glucose by rat diaphragm muscle. Of particular interest to the present studies is the factor identified in albumin containing protein fractions prepared from plasma of diabetic and pre-diabetic patients by Vallance-Owen and Lilley (1961). The albumin preparations used in our experiments to carry fatty acids did not show insulin antagonism. Moreover, there are several differences between the insulin insensitivity induced in muscle by fatty acids in these experiments and the insulin antagonism observed with albumin preparations by Vallance-Owen and Lilley: they are therefore unlikely to be the same. In particular the effects of fatty acids are much smaller and are seen in the absence of insulin added in vitro.

Mechanism and Physiological Significance of Effects of Fatty Acids and Ketone Bodies

These results and those of earlier studies in this laboratory have shown that agents which interfere with the formation of adenosine triphosphate (A.T.P.) by respiration accelerate three of the reactions involved in glucose metabolism in muscle, and that release of more fatty acids and ketone bodies for respiration slows them. The reactions involved are membrane transport and phosphorylation of glucose, and the phosphofructokinase reaction (Randle and Smith 1958, Morgan, Randle et al. 1959, Newsholme and Randle 1961, 1962). These reactions (and the pyruvate dehydrogenase reaction) may be regarded as the checkpoints in glucose metabolism in muscle. They are controlled by signals which transmit information about the balance of energy (A.T.P.) within the cell and the supply of fuel for respiration. An important question still to be answered concerns the nature of these signals. In earlier studies concerned with the influence of agents which interfere with the generation of A.T.P. the suggestion was made that the signal in this case was the concentration of A.T.P. in the cell. Direct evidence for this idea has recently been provided in the case of phosphofructokinase by Mansour et al. (1962) and Passonneau and Lowry (1962), who find that the enzyme is inhibited by A.T.P., and stimulated by adenosine monophosphate (A.M.P.) and inorganic phosphate (which are breakdown products of A.T.P. and precursors for synthesis of A.T.P. by respiration). Since we have been unable to detect any rise in the concentration of A.T.P., or fall in that of A.M.P. and inorganic phosphate, in rat hearts perfused with fatty acids or ketone bodies, a different signal may transmit information about these substrates. One possibility which might also explain the inhibitory influence of fatty acids and ketone bodies on pyruvate oxidation is inhibition of the enzymes concerned by acyl coenzyme A compounds (formed initially in the metabolism of fatty acids and ketone bodies). This, however, is a matter for future investigation.

These studies emphasise that the controlling influence of fatty acids and ketone bodies on carbohydrate metabolism in muscle is complex. Nevertheless it appears to be well suited for such physiological purposes as the conservation of blood glucose and muscle glycogen during starvation or dietary restriction of carbohydrate. The degree of impairment among the four steps affected seems to be most severe at the level of the pyruvate dehydrogenase reaction. This could perhaps allow glycolysis to continue its function as an important pathway for the synthesis of cell constituents during periods of carbohydrate deprivation while ensuring that the end products of glycolysis, pyruvate and lactate, are not oxidised but reconverted to glucose in the liver.

Summary

Evidence is presented that a higher rate of release of fatty acids and ketone bodies for oxidation is responsible for abnormalities of carbohydrate metabolism in muscle in diabetes, starvation, and carbohydrate deprivation, and in animals treated with, or exhibiting hypersecretion of, growth hormone or corticosteroids. We suggest that there is a distinct biochemical syndrome, common to these disorders, and due to breakdown of glycerides in adipose tissue and muscle, the symptoms of which are a high concentration of plasma non-esterified fatty acids, impaired sensitivity to insulin, impaired pyruvate tolerance, emphasis in muscle on metabolism of glucose to glycogen rather than to pyruvate, and, frequently, impaired glucose tolerance. We propose that the interactions between glucose and fatty-acid metabolism in muscle and adipose tissue take the form of a cycle, the glucose fatty-acid cycle, which is fundamental to the control of blood-glucose and fatty-acid concentrations and insulin sensitivity.

We wish to thank the British Diabetic Association, the British Insulin Manufacturers, and the Medical Research Council for support for this work. It is a pleasure to thank Prof. F. G. Young for his interest and encouragement.

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