NERVOUS AND HORMONAL CONTROL OF ADIPOSE TISSUE

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UNTIL quite recently adipose tissue was regarded as metabolically inert, its function limited to insulation and support and the passive storage of fat. Even after the classic work of Schoenheimer and Rittenberg (1937) had shown that adipose tissue participated in the continuous dynamic processes of the body, its role in energy metabolism continued to be accounted of far less importance than that of the liver. The modern era of revolutionary development in adipose tissue studies may be said to have begun with the review by Wertheimer and Shapiro in 1948 in which they concluded that adipose tissue was a specialised tissue supplied by a relatively dense capillary network and innervated by sympathetic nerve fibres, that deposition and mobilisation of fat were active processes involving the metabolism of the tissue, that synthesis of new fatty acids from carbohydrates proceeded continuously and that these metabolic activities were regulated by nervous and endocrine factors.

In the general survey which follows no attempt will be made to cite all the original publications on which it is based. Reviews published within the last four years include those of Wertheimer and Shafir (1960), Vaughan (1961), Jeanrenaud (1961), Winegrad (1962), Kinsell (1962), Steinberg (1963) and Renold and Cahill (1964).

The Metabolism of Adipose Tissue

Glucose metabolism. Glucose utilisation in adipose tissue as in muscle is regulated by the supply of intracellular glucose-6-phosphate. This, in turn, depends on the transport of glucose across the cell membrane and its phosphorylation in the presence of hexokinase and ATP. Phosphorylation of glucose is unlikely to be the rate-limiting step because adipose tissue hexokinase is saturated at extremely low concentrations of glucose, and it is therefore probable that the control of glucose metabolism is exerted at the level of glucose transport across the cell membrane. The problem of transport is complicated in adipose tissue by the existence of an active pinocytosis (Barnett and Ball, 1960), whose metabolic function is uncertain.

Glucose-6-phosphate is metabolised both by glycolysis and via the pentose phosphate shunt. The "shunt" is particularly active in adipose tissue and was, until recently, believed to be the major source of the reduced coenzymes necessary for the synthesis of fatty acids from glucose. According to Flatt and Ball (1963), however, only about half the coenzymes required are produced in the pentose cycle, the remainder being furnished during the conversion of triose phosphate to acetyl-CoA. This process indeed generates reduced coenzymes in far greater amounts than are needed to complete the reductive synthesis of fatty acids and this surplus must be oxidised if fatty acid synthesis is to proceed.

Glycogen storage and mobilisation are of relatively little importance in this tissue. Most of the carbon from labelled glucose is found in carbon dioxide, glyceride-glycerol and fatty acids. α -glycerophosphate, the precursor of glyceride-glycerol, is formed by reduction of dihydroxyacetone phosphate in the presence of NADH. It is important to note that adipose tissue cannot phosphorylate the glycerol made available by triglyceride breakdown and the rate of esterification of free fatty acids is thus regulated by the level of glucose metabolism in the tissue. Recent studies in man, however, suggest that glycerol may be conserved under some conditions (Carlson and Orö, 1963; Shafir and Gorin, 1963; Hagen Moorhouse and Steinberg, 1963).

Synthesis and hydrolysis of triglycerides

Glyceride synthesis requires the presence of both glycerol and fatty acids in an "activated" state and depends on the continuous production of energy in the form of ATP. Hydrolysis of triglycerides in adipose tissue is observed at two quite distinct points. Thus the incorporation of plasma glycerides into adipose tissue stores is preceded by their hydrolysis under the influence of lipoprotein lipase: this reaction is believed to occur at the cell surface. On the other hand, the hydrolysis of stored triglycerides is catalysed by a different lipase system, located within the cell and activated

by the presence in the tissue of hormones or lipolytic substances.

Mobilisation of fatty acids. Both synthesis and hydrolysis of stored triglycerides proceed continuously. The resting fat cell thus contains a pool of free fatty acids in dynamic equilibrium with stored triglycerides. Net accumulation of free fatty acids leading to their release into the circulation will result from either a decrease in the rate of synthesis or an increase in the rate of hydrolysis of triglycerides. Conversely, net deposition of triglycerides and suppression of fatty acid release will occur if the rate of synthesis is increased or the rate of breakdown is decreased.

Glycerol production. Considerable amounts of glycerol are produced in adipose tissue by hydrolysis of circulating as well as stored triglycerides. Studies of plasma glycerol concentration and turnover rate in the rabbit indicate that in the normal animal about 10 per cent of the calories used may be derived from glycerol. In the starved animal the value may be considerably greater (Hagen, 1963).

Effects of Hormones in Adipose Tissue

Most of the hormonal effects in adipose tissue can be explained on the basis of two principal sites of control. They are (1) the transformation of extracellular glucose into intracellular glucose-6-phosphate, and (2) the activity of the intracellular lipase system responsible for the breakdown of stored triglycerides.

Insulin. Since the presence of insulin augments all phases of glucose metabolism its primary effect is thought to be at the level of transport of glucose across the cell membrane, or, less probably, on its phosphorylation. Synthesis of glycogen, glycolysis, oxidation in the pentose cycle and synthesis of fatty acids are all increased: the production of increased amounts of α -glycerophosphate promotes storage of fatty acids as triglycerides and inhibits their release into the circulation. Similar effects are produced by increasing the concentration of glucose to which the tissue is exposed, provided some insulin is present. Lack of insulin inhibits glucose uptake and lipogenesis, and favours the release of free fatty acids into the circulation. Despite the acceleration of glucose metabolism by insulin and glucose, the oxidation of acetyl-CoA in the Krebs cycle is not increased and may actually be reduced (Flatt and Ball, 1963). The partial

shutdown of the cycle may be a compensatory mechanism permitting re-oxidation of the surplus reduced coenzymes produced during the process of converting glucose into fat.

The metabolic effects of insulin in adipose tissue are associated with remarkable ultrastructural changes (Barnett and Ball, 1960). When rat adipose tissue which has been incubated *in vitro* in the presence of insulin and glucose is examined with the electron microscope the cytoplasm is found to have changed from a granular to an agranular state and to have become filled with membrane-bound vesicles. The mitochondria have become elongated and pleomorphic and free lipid inclusions have appeared in the cytoplasm. The plasma membrane is seen to be indented at many sites to form finger-like invaginations and beneath it lie numerous tiny vesicles suggesting that pinocytosis is occurring.

While insulin is certainly the most important agent regulating glucose metabolism and lipogenesis it must be noted that similar effects have been produced under certain experimental conditions with prolactin and with oxytocin.

Lipolytic substances. A large number of substances has been shown to be capable of releasing fatty acids from adipose tissue. They include (1) catecholamines—adrenaline, noradrenaline and certain analogues; (2) glucagon; (3) FMS—a fat-mobilising substance found in fasting urine (Chalmers, Pawan and Kekwick, 1960; Chalmers, 1964); (4) pituitary substances—growth hormone, ATCH, TSH, FSH, α - and β -MSH and arginine vasopressin; and a number of lipolytic peptides isolated from pituitaries, namely “fraction H” (Rudman, Reid, Seidman di Girolamo and Bern, 1961), “peptide I” (Friesen, Barrett and Astwood, 1962) and “lipotropin” (Li, 1964). The structure of peptide I has been partially elucidated and it is shown to be a derivative of pig β -MSH (Hofmann and Katsoyannis, 1963). Lipotropin has 59 amino acids and a molecular weight of 6,600. A number of synthetic peptides related to corticotropin also have adipokinetic activity (Raben, Landolt, Smith, Hofmann and Yajima, 1961).

These agents liberate fatty acids from adipose tissue by directly augmenting the lipolytic reaction. Rizack (1961) succeeded in isolating the intracellular lipolytic system in cell-free preparations and showed that its activity was enhanced by previous treatment with adrenaline as well as by starvation. Activity lost as a result of incubation could be restored by addition of adrenaline and ATP. Similar effects

have been obtained with ACTH, TSH and glucagon.

Consideration of the diversity of molecular structures capable of stimulating the lipolytic reaction led to the suggestion that peptide hormones such as ACTH might act indirectly by releasing or activating catecholamine stored in the tissue (Paoletti, Smith, Maickel and Brodie, 1961). However, contrary to earlier belief, the response to ACTH is not abolished by depletion of catecholamine stores (Edmonson and Goodman, 1962; Ho and Meng, 1964). Blocking the response to adrenaline with DCI (dichloro-isoproterenol) does not inhibit the lipolytic effect of ACTH *in vitro* (Goldiner and Chalmers, unpublished). And neither ganglionic nor adrenergic blockade interferes with the mobilisation of free fatty acids by growth hormone in monkeys. Moreover the adipose tissue of rabbits and guinea-pigs is highly sensitive to certain pituitary peptides but quite insensitive to catecholamines.

Another possible mode of action common to both catecholamines and peptide hormones is through adenosine-3',5'-phosphate or 3',5'-AMP. This substance is believed to be concerned in the action of hormones in many tissues, for example in glycogen breakdown by adrenaline and glucagon in liver and in steroidogenesis by ACTH in adrenal cortex (Sutherland, 1962). Accumulation of 3',5'-AMP in a particulate fraction of adipose tissue is enhanced by adrenaline, and 3',5'-AMP itself activates the adrenaline-sensitive lipolytic system (Rizack, 1964). Addition of 3',5'-AMP to the medium in which adipose tissue is incubated causes, however, none of the changes produced by adrenaline under similar conditions. This does not, of course, exclude the possibility that the nucleotide formed *within* the tissue plays a role in the effects of adrenaline and certain other hormones (Vaughan, 1961).

There are considerable species differences in the responsiveness of adipose tissue to lipolytic hormones. Rabbit and guinea-pig adipose tissues are highly responsive to nearly all the pituitary peptides listed but unresponsive to catecholamines and FMS. Rat, dog and probably mouse and hamster adipose tissues respond only to certain pituitary substances but are highly sensitive to FMS and catecholamines. Pig adipose tissue has so far proved unresponsive to all substances tested (Rudman, Brown and Makin, 1963). Human adipose tissue probably behaves like rat and dog: thus it is known to respond to catecholamines, FMS and growth hormones, but not to peptide I or

fraction H. Variations in sensitivity among different species may be due to inactivating enzymes (Rudman, Malkin, Brown, Garcia and Abell, 1964). Rat adipose tissue contains an enzyme capable of inactivating ACTH and rabbit adipose tissue inactivates α -MSH; however, in both cases a lipolytic response occurs.

Besides their primary effect on the lipolytic mechanism these hormones produce characteristic changes in glucose metabolism believed to be mediated by a rise in the intracellular concentration of fatty acids, and consisting in (1) an increase in glucose uptake and an increase in the incorporation of glucose carbon into glyceride-glycerol (2) a relative decrease in the metabolism of glucose over the pentose pathway, and (3) an increase in the oxidation of glucose by the Krebs cycle (Lebeuf and Cahill, 1961). In addition, in the presence of insulin there is an even greater increase in glucose incorporation into glyceride-glycerol and the insulin effects on glycogen and fatty acid synthesis are inhibited. The increased incorporation of glucose into glyceride-glycerol is interpreted as evidence of increased re-esterification of fatty acids. A large and sustained increase in oxygen consumption accompanies this rapid hydrolysis and re-synthesis of triglyceride within the tissue (Bart and Jungas, 1961) and it is possible that heat generated in this way may at times contribute to the maintenance of body temperature. Thus Dawkins and Hull (1963) have shown that in the new-born rabbit exposed to cold the temperature in brown fat may exceed the colon temperature by as much as 2°C.

Physiological Role of Hormones

Studies in intact animals and clinical and experimental observations in man confirm that insulin and glucose are the major regulators of fat accumulation. In obese subjects, both diabetic and non-diabetic, excessive insulin production has been repeatedly demonstrated (Rabinowitz and Zierler, 1962; Hales and Randle, 1963; Grodsky, Karam, Pavlatos and Forsham, 1963). Administration of insulin or glucose also promptly reduces the V-A difference of free fatty acids (FFA) in perfused adipose tissue and lowers plasma FFA levels in intact animals, including man. This immediate response is presumably due to increased esterification of FFA in adipose tissue.

Although there is still much uncertainty about the physiological role of lipolytic hormones, it is becoming clear that the activity

of the *sympathetic nervous system* is a major factor in determining the levels of both FFA and other lipid fractions in plasma. Electrical stimulation of nerves supplying adipose tissue increases the output of FFA, presumably through release of noradrenaline at the nerve-endings; whereas denervation of adipose tissue reduces its ability to mobilise its lipid during fasting. Ganglionic blockade reduces plasma FFA levels in the dog. Infusion of adrenaline or noradrenaline in man produces a prompt elevation of plasma FFA: this effect can be abolished by pronethalol. Similarly, the sympathetic discharge associated with emotional stress can markedly raise plasma FFA levels; the relative contributions of sympathetic nerves and adrenal medulla to this response are not known. Nestel (1964) has shown that fasting plasma triglyceride levels may be correlated with the increment in plasma FFA following noradrenaline infusion in both normal subjects and those with coronary heart disease.

Thyroid and adrenocortical hormones have been shown to have important indirect effects on fat mobilisation. The response to adrenaline is markedly impaired both *in vivo* and *in vitro* in adrenalectomised animals and can be restored by pre-treatment with cortisone. The permissive effect of cortisone is obtained with doses that do not by themselves alter plasma FFA levels: a direct lipolytic effect may be obtained *in vitro* with rather high concentrations. A similar permissive effect of triiodothyronine has been shown in hypophysectomised monkeys: in this case glucocorticoids alone were without effect on the adrenaline response. (Harlan, Laszlo, Bogdonoff and Estes, 1963, a, b) have shown that the response of plasma FFA to infusions of adrenaline and noradrenaline is increased in hyperthyroidism and decreased in hypothyroidism. Hyperthyroid patients tend to have elevated plasma FFA levels.

The extent to which *pituitary hormones* are more directly involved in fat mobilisation is less clear and may well vary in different species. In man there are strong grounds for assigning an important role to *growth hormone*. The administration of human growth hormone (HGH) causes a large increase in plasma FFA, the response being relatively slow and long-lasting in comparison with that elicited by catecholamines. Recent studies of HGH secretion (Jansz, Doorenbos and Reitsma, 1963; Roth, Glick, Yalow and Berson, 1963) indicate that fasting and hypoglycaemia are associated with high plasma HGH levels and that the adminis-

tration of glucose causes an abrupt fall in plasma HGH levels. HGH concentration in plasma also rises when the uptake of glucose is blocked by 2-deoxyglucose and after muscular exercise. Hunter and Greenwood (1964) found the half-life of endogenous HGH to be about 20 mins. These studies establish the existence in man of a mechanism for controlling the secretion of growth hormone sensitive to the availability of intracellular glucose and capable of fairly rapid responses.

There is still considerable doubt about the precise mode of action of growth hormone in adipose tissue. *In vitro*, concentrations of the order of 100 $\mu\text{g/ml}$. are required to obtain a lipolytic response, whereas ACTH is effective at 0.01 $\mu\text{g/ml}$. or even less. Vaughan and Steinberg (1963) re-investigated this problem and concluded that any lipolytic effect of growth hormone preparations *in vitro* could be accounted for by traces of TSH. The lipolytic effect of growth hormone *in vivo* may therefore be due to the production of another substance capable of acting directly in adipose tissue. Such an agent could be formed from growth hormone itself by the action of a proteolytic enzyme; or it might be released from a target organ. Mechanisms involving glucagon release or interference with the action of insulin appear to be ruled out by the well-known ketogenic effect of growth hormone in the depancreatized dog.

Chalmers and others (1960) have reported that during fasting or restriction of carbohydrate intake the urine of man and certain other mammalian species contains a potent fat-mobilising substance (FMS) of low molecular weight. The pituitary or adjacent hypothalamus is necessary for the production of this material; but it differs from known pituitary adipokinetic substances including fraction H, peptide I and lipotropin. The active principle has not yet been obtained in pure form and its chemical nature is unknown. It has not been detected in the urine of hypophysectomised subjects after administration of HGH, but appears to be produced in excess by some patients with acromegaly (Chalmers, 1964). Its relationship to growth hormone will therefore require further elucidation. FFA-releasing activity has been reported in serum from fasting normal subjects and untreated diabetics (Recant, Alp, Koch and Eggeman, 1963). The active substance is non-dialysable but it may prove to be FMS in bound form.

Madison, Mebane, Unger and Lochner (1964) have recently provided evidence for a stimulatory feedback of ketones on pancreatic

beta cells. The infusion of ketones into normal dogs produces effects resembling those of a slow infusion of insulin. These effects are not seen in depancreatized dogs. Both intravenous and direct pancreatic infusion of ketone bodies cause an increased secretion of insulin into the pancreatic vein. The effect of this mechanism in prolonged starvation would be to modulate the release of FFA from adipose tissue and to regulate the rate of ketone production by the liver, and thereby to prevent the development of progressive ketoacidosis by establishing a new steady state.

Conclusion

Insulin and glucose have a threefold effect on adipose tissue metabolism. Firstly, they

control the rate of lipogenesis; secondly, they influence FFA-release through their effect on re-esterification; and lastly, by their action on cerebral metabolism they control the secretion of growth hormone and help to regulate sympathetic nervous activity. It is likely that the sympatho-medullary system functions mainly as a rapid and short-acting fat-mobilising mechanism, while the pituitary provides for a slower and more sustained response which may be modulated during prolonged starvation by a ketone-insulin feedback. The role of glucagon and of pituitary lipolytic substances other than growth hormone is at present uncertain. Important indirect effects on fat mobilisation are exerted by the thyroid and adrenal cortex.

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