

INFLUENCE OF HORMONES ON LIPID METABOLISM

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Recent advances in biochemical tools and techniques have helped to open up many hitherto uncharted areas of intermediary metabolism and have made feasible more intimate studies of biochemical lesions in various endocrine states. The literature on the possible hormonal control and direction of specific intracellular reactions is both vast and confusing. Many investigators have used crude hormone preparations or studied certain enzyme systems, not because these enzymes were most directly involved from the physiological point of view, but because they were more easily estimated. In many studies it is difficult to establish a direct relationship between a certain investigative treatment and the results obtained. Too many papers in this field continue to give unmerited importance to the peripheral alterations in enzymes in endocrine disease instead of trying to elicit information from the basic reactions involved in the endocrine disorder. In the present paper, an attempt is made to present an integrated view of the influence of hormones on the enzymes of lipid metabolism.

Before going into details of enzymatic steps where a stimulatory or inhibitory influence of a hormone is noticeable, one should stress the limitations of the 'biochemical approach' in the attempts at elucidation of the action of any hormone (Hechter, 1955). Many investigators favour the view that most metabolic influences of hormones can be explained by alterations in permeability of target cells, instead of specific enzymes being directly stimulated or restrained. Though the permeability hypothesis has some virtue in a few cases, it should be remembered that the process of permeation itself is effected enzymically (Cohen and Monod, 1957 ; Jacob and Monod, 1961). Even if permeation was non-enzymic, there is also the question whether in every case, transport of a substrate and its metabolic transformation, are necessarily related as cause and consequence. On the other hand it seems more reasonable to visualize hormonal direction and control of metabolism in terms of their participation in enzymic reactions. Much support to such thinking is afforded by the occurrence of many physiologically meaningful biochemical and

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enzymatic alterations in endocrine diseases (DiPietro and Weinhouse, 1960; Yielding and Tomkins, 1959; Jensen, 1959; Rosen *et al.*, 1959; Matthes *et al.*, 1960). It is difficult, however, to accurately pin point the locus of hormonal effect in a series of biochemical reactions because of the amazing capacity of biological systems to amplify and elaborate on a disturbance at a molecular level. However, reasonable justification for efforts to extrapolate enzymatic findings to the whole organisms, is afforded by the recent *in vitro* demonstration of hormonal effects (not always in physiological concentrations) on many enzyme systems (Talalay *et al.*, 1958; Hagerman and Villet, 1959; Sutherland and Rall, 1960).

BIOCHEMISTRY OF LIPID METABOLISM

Fatty acid oxidation—The complete oxidation of fatty acids into carbon dioxide and water involves the following six enzymatic sequences (Lynen, 1957). (i) The activation of the fatty acid with CoA and ATP to form fatty acyl CoA, there being three different enzymes, responsible for the activation of fatty acids of different chain lengths. (ii) The conversion of fatty acyl CoA to $\alpha\beta$ unsaturated fatty acyl CoA in the presence of FAD, which may also involve more than one enzyme. (iii) The enzymic addition of a molecule of water to the $\alpha\beta$ unsaturated derivative to form the corresponding β hydroxy fatty acyl CoA. (iv) The oxidation of β hydroxy fatty acyl CoA derivative to the β ketofatty acyl CoA in the presence of DPN (or TPN). (v) The thiolysis of β keto fatty acyl CoA in the presence of CoA to give acetyl CoA and a fatty acyl CoA containing two carbons less than the original fatty acid. (vi) The condensation of acetyl CoA with oxaloacetate to form citrate to initiate the complete oxidation of acetate to carbon dioxide and water through the Krebs cycle. Acetyl CoA can also condense with itself to form acetoacetyl CoA and this AcAc CoA is enzymically deacylated to form AcAc (Drummond and Stern, 1960). In addition, acetyl CoA can also condense with AcAc CoA to form HMG CoA, which can then be cleaved to form AcAc (Lynen *et al.*, 1958). Acetoacetate can be activated to form AcAc CoA in the muscle but in the liver the AcAc activating enzyme is very weak. Also AcAc can be reduced by a dehydrogenase present in the tissues to form D(—) β

Abbreviations used: acetate, Ac; acetoacetate, AcAc; coenzyme A, CoA; β hydroxy β methyl glutarate, HMG; diphosphopyridine nucleotide, DPN; triphosphopyridine nucleotide, TPN; reduced diphosphopyridine nucleotide, DPNH; reduced triphosphopyridine nucleotide, TPNH; cyclic adenosine 3'-5'-monophosphoric acid, cyclic AMP; growth hormone, GH; adrenocorticotrophic hormone, ACTH; free (unesterified) fatty acids, FFA; flavin adenine dinucleotide FAD; thyrotrophic hormone, TSH.

hydroxybutyric acid or decarboxylated to form acetone or reconverted to AcAc CoA by transferase reactions with succinyl CoA or malonyl CoA in the muscle. (Stern *et al.*, 1956; Menon and Stern, 1960). The transferase is not present in the liver. The turnover numbers of the fatty acid oxidizing enzymes are such that the β keto fatty acyl compounds (eg. AcAcCoA) are formed at a much greater rate than they are metabolized by subsequent reactions (Mahler, 1953). It should be mentioned that in addition to the activation, transferase and thiolase type reactions, fatty acyl CoA derivatives can also be formed in the body by the oxidative decarboxylation of α ketoacids (Jagannathan and Schweet, 1952; Kaufmann *et al.*, 1953). CoA and DPN (or TPN) dependent oxidation of aldehydes (Burton and Stadtman, 1953; Yamada and Jakoby, 1959) or aldol type cleavage of acyl coenzyme A esters (Bacchawat *et al.*, 1955).

Fatty acid synthesis—Though the synthesis of fatty acids, not too long ago was thought to take place by the reversal of the series of reactions responsible for fatty acid oxidation, recent evidence suggests that as in carbohydrate metabolism, in fatty acid metabolism also, the catabolic and anabolic pathways are different (Cornforth, 1959). According to one of the suggested mechanisms of fatty acid synthesis, acetyl CoA is first carboxylated to give malonyl CoA (Wakil, 1958) which then condenses with another molecule of acetyl CoA to give acetomalonyl CoA (Wakil and Ganguly, 1959). Acetomalonyl CoA is presumably then reduced by an enzyme requiring TPNH as cofactor to ethyl malonyl CoA, which can then be decarboxylated to give butyryl CoA (Stern *et al.*, 1959, 1961). The process is continued till a C_{18} or C_{16} fatty acid is formed (Brady *et al.*, 1960). It is likely that coenzyme A esters of higher fatty acids, e.g. stearyl CoA, do not condense with malonyl CoA unlike esters of fatty acids of medium chain length (Brady, 1960; Brady *et al.*, 1960), thus accounting for the physiological preponderance of C_{16} and C_{18} , fatty acids. Many interdigitating contacts between the substrates available from fatty acid and aminoacid oxidation, and the substrates required for fatty acid synthesis are afforded by the presence of carboxylating enzymes for acetyl CoA, butyryl CoA and hexanoyl CoA as well as transferases to malonic semi-aldehyde (Menon *et al.*, 1960), and probably other aldehydes like succinic semi aldehyde and glutaric semialdehyde.

Cholesterol synthesis—The cholesterol synthesis in the organism occurs by the following series of reactions (Lynen, 1959; Lynen *et al.*, 1959).

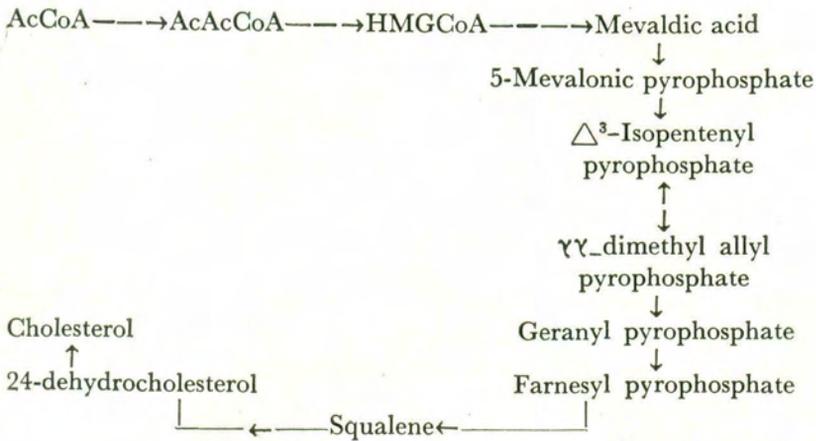


Fig. 1. Steps in the biosynthesis of cholesterol

The high level of HMGC CoA reductase in microsomal preparations from triton treated and the low level from fasting rat livers is in accord with the incorporation of acetate to cholesterol in such preparations. It is likely that this enzyme is important in the physiological control of hepatic cholesterol synthesis (Bucher *et al.*, 1960) and supports the previous finding of Migicovsky, of a block between HMG and squalene in starvation (Scaife and Migicovsky, 1957. Triparanol (Mer 29) inhibits the conversion of 24-dehydrocholesterol to cholesterol, and vanadium the conversion of HMGC CoA to Δ^3 -Isopentenyl pyrophosphate (Azarnoff and Curran, 1957).

LIPOLYTIC AND LIPID MOBILISING EFFECTS OF HORMONES

Apart from their probable role in the oxidation or synthesis of fatty acids, many hormones exert a lipid mobilising or lipolytic effect. When GH is administered to fasting animals, large amounts of body fat are mobilised in the liver, (Szego and White, 1949) though the total carcass fat of fed rats receiving GH for long periods is reduced. The adrenalectomized animal's ability to transport fat to the liver is noticeably impaired. Thus, fatty infiltration of the liver is less in adrenalectomized than in normal control animals, irrespective of whether the condition is induced by high fat or alipotrophic diets or administration of pituitary extracts or hepatotoxic agents. In addition to GH and ACTH, Rudman *et al.*, (1960), have recently acquired evidence that a distinct polypeptide pituitary hormone with lipid mobilising activity also exists.

The lipid depleting action of ACTH on the adrenal cortex (Engel, 1957) requires calcium ions, as also does the steroidogenic effect of ACTH on adrenal slices (Peron and Koritz, 1958; Lopez *et al.*, 1959), whereas the lipolytic effect of epinephrine and nor-epinephrine or growth hormone is not Ca^{++} dependent (Bally *et al.*, 1960). Glucose or insulin inhibits the lipolytic effect in all cases (Dole 1956; Gordon 1957). The alterations in lipid metabolism induced by starvation, by feeding of glucose, by insulin deficiency or by adaptation to high fat diets are restricted to changes in the metabolism of long chain fatty acids and not of short chain fatty acids (except in lactating mammary gland) (Fritz, 1961; Langdon, 1960). Though some long chain FFA may arise in part from intravascular lipolysis mediated by heparin activated lipoprotein lipase (Robinson and Harris, 1959), most of plasma FFA is derived from adipose tissue and is transported to the liver (Fritz, 1961). Thus the FFA released into the liver through the action of ACTH, epinephrine or GH swamp the FFA pool of the liver, producing enhanced fatty acid oxidation and ketogenesis (Langdon, 1960). The presence of an increased FFA pool in the liver can also account for the decreased fatty acid synthesis under these conditions by a feed back inhibition mechanism.¹

According to this mechanism, the lipogenic influence of insulin and the ketogenic effect of other hormones are ascribed to their control over the FFA pool in the liver rather than to an acceleratory or inhibitory effect on any specific enzymic step. This hypothesis has the virtue of multivalent approach in explaining both lipid synthesis and oxidation in terms of feed back control and providing a rationale for the similar effects of such different substances like ACTH, GH and epinephrine. Inhibition of lipolysis by glucose is presumably through formation of α glycerophosphate by glycolysis thus stimulating triglyceride synthesis.

LIPID METABOLISM IN DIABETES

Fatty acid oxidation—The impaired ability of the diabetic organism to synthesize fat and the ketonemia and ketonuria characteristic of untreated diabetes have attracted the attention of biochemists and physiologists since a long time. There is no failure in the diabetic animal to produce acetyl CoA, since ketone bodies are readily formed from fatty acids (Stadie, 1954). The

¹ The retro-inhibition, involves the inhibition of input by output i.e. the inhibition of activity of an early enzyme in an anabolic sequence (e.g. enzymes bringing about fatty acid synthesis) by the ultimate product of the sequence (e.g. fatty acids released from adipose tissue into the liver). This biological phenomenon was first described by Novick and Szilard (Novick 1955) and has since then, been observed frequently (Yates and Pardee, 1956; Umbarger 1956; Jacob and Monod, 1961).

enhanced synthesis of acetoacetate in diabetes is not due to a deficiency of oxaloacetate (Shaw and Tapley, 1958). Total respiration is not depressed in tissues from diabetic organisms (Weinhouse, 1952), in fact fructose, lactate, and pyruvate are oxidized as well in the diabetic organism as in the normal. These findings suggest no gross impairment of the Krebs cycle. A definitive decrease in the capacity for oxidative phosphorylation in diabetic mitochondria has been reported (Haugaard *et al.*, 1951), but it seems more reasonable to attribute any such impairment in the diabetic liver to fatty infiltration *per se* and not to diabetes. Hence, the increased ketone synthesis in the diabetic liver must be due to either an increased production of AcAc from AcCoA, AcAcCoA or HMGCoA, or increased production of AcCoA itself or its decreased utilisation for fatty acid synthesis. Weiland *et al.*, (1956) observed that in alloxan diabetic rats, the activities of β ketoacyl-thiolase, β -hydroxyacyl dehydrogenase and acyldehydrogenase of liver were increased on an average of 17 per cent, 39 per cent and 115 per cent respectively. Also both acetoacetyl CoA deacylase and HMGCoA cleavage enzyme are markedly elevated in diabetes, (Segal and Menon, 1960, 1961). These do not necessarily indicate new enzyme synthesis, since apparent and not total activities were being measured. When total activities are measured by treatment of tissues by detergents or by freezing and thawing, the differences in enzyme activities between normal and diabetic tissues almost disappear, indicating that in diabetes, increases in enzyme activities occur, not due to changes in the enzyme content, but due to easier extractibility of the enzymes from cellular sites in diabetes (Segal and Menon, 1961). The HMG

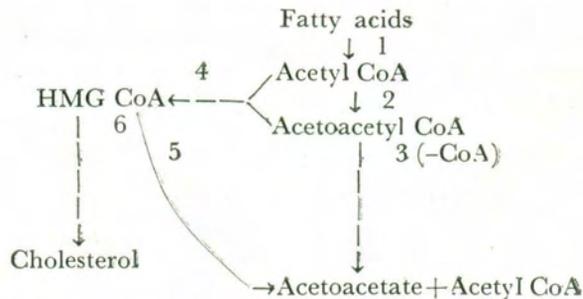


Fig. 2. *Ketogenesis in the liver*

CoA condensing enzyme (reaction 4) on the other hand, is not increased in diabetes (Menon, unpublished observations). The physiological aspects of ketosis, particularly the influence of hormones has been reviewed by Campbell and Best (1956). It has been pointed out that the ketone utilization by the muscle is independent of insulin; hence the increased ketosis of diabetes

must be mainly due to over production of ketones by the liver rather than under-utilisation by the muscle (Campbell and Best, 1956). Also insulin treatment affects only ketogenesis from glycerides of long chain fatty acids (Lossow *et al.*, 1956); this and the absence of an insulin effect on thiolase and coenzyme A transferase (Menon, unpublished observations) reactions suggest strongly that the very high ketogenesis of diabetes is due to an increase in FFA release rather than to a specific enzymic stimulation of the pathway of acetoacetate production. The FFA so released, activates adenosine triphosphatase (Pressman and Lardy, 1956), uncouples oxidative phosphorylation in the mitochondria and thus introduces many other ancillary changes in metabolism characteristic of the diabetic state. This explains why ketosis in the intact animal is almost invariably preceded by the development of fatty liver. This also explains why lower fatty acids are more ketogenic than long chain fatty acids, for the former are poor substrates for the enzymes catalyzing triglyceride and phospholipid synthesis (Kennedy, 1957).

Fatty acid synthesis—Block and Kramer (1948) first showed that insulin *in vitro* stimulated the incorporation of acetate (in the presence of pyruvate) into fatty acids of liver slices from rats, whereas it has no effect on the incorporation of butyrate or caproate (Brady and Gurin, 1950). This suggested a metabolic block in the conversion of acetate to butyrate in diabetes. Shaw *et al.*, (1957) showed that some reaction before butyryl CoA formation could be a limiting step in fatty acid synthesis in mitochondrial extracts. In view of the specific requirement for TPNH for the reduction of crotonyl CoA (Langdon, 1957) and in view of indications of decreased generation of TPNH in diabetes (Milstein, 1956; Siperstein, 1957) it has been postulated that the biochemical lesion in fatty acid synthesis is due to decreased availability of TPNH (Siperstein, 1958). Matthes *et al.*, (1960) have found a specific lesion in the synthesis of fatty acids in diabetes in the TPNH requiring ethylene reductase. These findings may indicate that the cell responds to TPNH deficiency by shutting down fatty acid synthesis and probably favoring cholesterol biosynthesis for the latter requires less TPNH (Layne *et al.*, 1960). Abraham *et al.*, (1959, 1960) on the other hand find that generation of TPNH was the same in diabetic and normal liver preparations; yet lipogenesis in diabetes is only a fraction of the normal. Also citrate addition stimulated lipogenesis more than did glucose-6-phosphate, under conditions where both substrates formed the same amount of TPNH. As a result of comparison of the enzymic steps involved in the synthesis of fatty acid from acetate in the normal and diabetic rat livers, Chaikoff and Coworkers (Abraham

et al., 1960, Matthes *et al.*, 1960) have concluded that (i) the acetate activation is the same in normal and in diabetic liver homogenates and ii) defective lipogenesis observed in the diabetic liver homogenate is not due to deficiency cofactors like CoA, ATP, Mg^{++} , TPN or DPN.

EFFECTS OF ADRENALECTOMY, ADRENOCORTICOTROPHIC HORMONE AND CORTICOID TREATMENT

Since the classical investigations of Long and Lukens (1936), the ameliorative effect of adrenalectomy on the diabetic organism has been well recognised. The beneficial effect of adrenalectomy on diabetics is considered to be due to the lack of gluconeogenesis in the absence of corticoids. The ketonemia and ketonuria of pancreatectomy is reduced in adrenalectomized animals (Stadie, 1954). Whether this effect is due to an increase in the utilisation of ketone bodies or their decreased production is not clear; however the decreased production of ketones from fatty acids by liver of adrenalectomized rats, indicates certainly an impairment of some step in the oxidation of fat, for there is practically no utilisation of ketones in this tissue.

Haynes (1958) observed that the steroidogenic effect of ACTH in the adrenals could be duplicated by cyclic AMP implicating this nucleotide in initiating corticoidogenesis. According to Haynes ACTH elicits the liberation of cyclic AMP, thereby activating phosphorylase of the adrenal cortex. As a result glycogenolysis occurs facilitating the generation of TPNH according to Fig. 3. ACTH has also another action on the adrenal cortex independent of cyclic AMP mediated glycogenolytic effect; this consists in the calcium dependent enzymic liberation of cholesterol from cholesterol esters. The lipolytic and steroidogenic effect of ACTH in adrenals may be schematically presented as follows:—

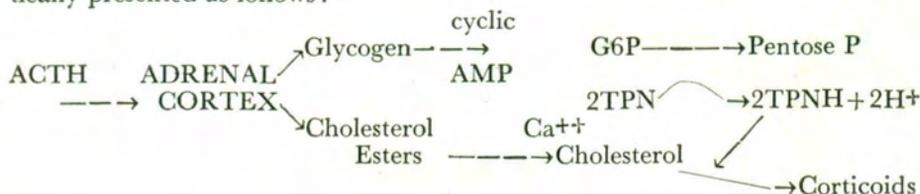


Fig. 3. Corticoidogenesis by ACTH

That hormone stimulated synthesis of cyclic AMP does not of itself stimulate FFA release is indicated by the recent work of Vaughan (1960 a). The TPNH requirement for corticoid hormone synthesis in the adrenal cortex has been well established (Halkerston *et al.*, 1959, 1961, Constanto-

poulos, and Chen, 1961). The question as to whether the primary effect of ACTH on the adrenal cortex is on its carbohydrate or lipid metabolism, is not certain. In the rat epididymal fat tissue however, there is evidence to support the view that the lipolytic effect of ACTH precedes the hormonal influence on glucose metabolism (Leboeuf and Cahill, 1961).

The characteristic deposition of fat induced by administration of cortisone is partly due to enhanced gluconeogenesis from protein and partly due to suppression of ACTH release which results in the inhibition of fat movement from the depot (Levy and Ramey, 1959).

INFLUENCE OF EPINEPHRINE

Sutherland and Rall (1957, 1958, 1960), Sutherland *et al.*, (1958) have established that the glycogenolytic effect of epinephrine and glucagon in the liver are brought about through the mediation of cyclic AMP. It is doubtful whether the lipolytic effect of epinephrine is mediated through the generation or release of cyclic AMP, for there is no correlation between the effect of hormones on phosphorylase and the release of FFA (Vaughan, 1960b). In the rat epididymal fat tissue, the lipolytic effect of epinephrine like that of ACTH is independent of active glycolysis (Lynn *et al.*, 1960). It has been well recognized that fatty acids are stored almost exclusively as triglycerides in adipose tissue (Miller and Cooper 1958), but released as free fatty acids. The lipid mobilising influence of epinephrine and other hormones like ACTH and GH may be effected through an activation of a lipase. Raizack (1961) has recently observed an elevation in the lipase of epididymal fat pad of rats during starvation or incubation of the tissue with epinephrine. 'Inactive' lipase of tissue could be activated by incubation with either epinephrine plus a sediment prepared from the tissue or epinephrine plus ATP. Though, in general there is an inverse relationship between the release of free fatty acids and the uptake and utilisation of glucose, it should be emphasized that the epinephrine stimulated fatty acid release is accompanied by an increased glucose uptake. The reason for this is at present unknown.

GROWTH HORMONE EFFECTS

It has long been recognised that administration of GH to animals induces a period of fat catabolism and ketosis simultaneous with the period of growth. Conversely changes of respiratory quotient indicative of a decrease in fat catabolism are associated with a slowing or cessation of growth (Greenaum, 1953). GH therapy can induce ketosis (Campbell and Davidson, 1951);

GH treated animals exhibit increases in oxygen consumption or in ketone body formation. These metabolic effects GH are best demonstrated in animals fed with fat (Russell, 1957). Best and coworkers are of the opinion that GH exerts its anabolic effect from energy obtained by the catabolism of fats, even as insulin exerts an anabolic effect from energy obtained from the oxidation of carbohydrates. The parallelism between insulin and GH may go further. Many investigators maintain that the primary action of insulin is on carbohydrate metabolism. All other effects of the hormone on fat or protein metabolism are secondary to its effect on the oxidation of glucose. Similarly it appears that the primary effect of GH is in the derivation of energy from the oxidation of fat; other metabolic changes occur subsequently. The increased ketonemia in GH treated animals is not due to any effect of the hormone on the rate of utilisation of ketone bodies (Bennett *et al.*, 1948) and is, from all evidence available due to an increased catabolism of fatty acids (Ketterer *et al.*, 1957). Further work with GH treated animals showed that there is no increase in acetoacetate synthesis from AcAc CoA (Segal and Menon, 1961), indicating that the ketogenic action of GH may be either a sequel to increased mobilisation from the adipose tissue or due to activation of some enzymic reaction between fatty acid and acetoacetyl coenzyme A. GH has a lipolytic effect similar to that of ACTH in adipose tissue (Leboeuf and Cahill, 1961).

EFFECT OF THYROXINE

Feeding of desiccated thyroid to rats results in an increased number of mitochondria per unit of tissue (Lardy and Maley, 1954) and hence increased oxidation of fat. Also thyroxine produces an inactivation of malic dehydrogenase and consequently a failure of oxaloacetate formation (Wolff and Ball, 1957), thereby facilitating ketogenesis. It has been known for many years that thyroid treatment increases many respiratory enzymes. Lardy *et al.*, (1960) showed that thyroid feeding induced an almost twentyfold increase in rat liver mitochondrial α glycerophosphate dehydrogenase; this was shown to be due to the synthesis of new dehydrogenase protein rather than activation of a latent form of the enzyme. In contrast to the great increase in mitochondrial α glycerophosphate dehydrogenase, the amount of soluble dehydrogenase is not at all affected by feeding of thyroid. Hence the net result will be increased availability of DPNH in the mitochondria, since DPNH cannot freely diffuse out of the mitochondria, whereas α glycerophosphate and dihydroxyacetone phosphate can.

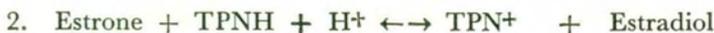
Phillips and Langdon (1956) found that thyroid supplements doubled the liver soluble TPNH-cytochrome C reductase, and postulated that the

function of the thyroid hormone is to enhance the oxidation of extramitochondrial pyridine nucleotide. However, DPNH-cytochrome C reductase is not elevated in hyperthyroid livers (Phillips and Langdon, 1956). Since TPNH is required in nonmitochondrial fatty acid synthesising systems, this effect of thyroxine may probably account for the reduced fatty acid synthesis in hyperthyroid animals. Conversely the lipoidosis and hypercholesterolemia of myxœma may represent the biochemical manifestation of enhanced TPNH availability in this condition. The suggested inhibitory effect of thyroxine on the transhydrogenase reaction: $DPN^+ + TPNH \leftrightarrow TPN^+ + DPNH$, attributes to this hormone, a directive role in the canalisation of metabolic pathways away from phosphorylation coupled oxidations of DPNH (Ball and Cooper, 1957). In addition many investigators believe that thyroxine has a direct effect on mitochondria (Emmelot and Bose, 1958) and causes uncoupling of phosphorylation and it is likely that these effects may involve chelation of Mg^{++} by the hormone.

EFFECTS OF ESTROGENS

It has been pointed out that phospholipid metabolism of the uterus constitutes a very sensitive indicator of early estrogen action; the stimulatory effects *in vivo* and *in vitro* of estradiol and related estrogenic hormones on metabolic pathways leading to lipid synthesis in the rat uterus has been recently reported by Aizawa and Mueller (1961).

Two groups of investigators (Talalay and Williams-Ashman, 1958; Vilee and Hagerman, 1959) have ascribed to estrogens the function of catalysing the enzymic transfer of hydrogen between DPN and TPN, although the mechanism of this reaction is controversial (Tepperman and Tepperman, 1960). The Talalay—Williams—Ashman hypothesis of the participation of estrogens in the transhydrogenation reaction may be represented thus

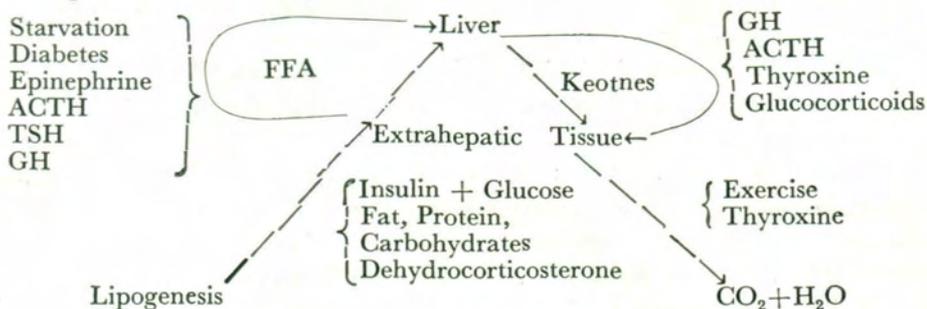


By controlling the electron the shuttle between DPN and TPN according to equation 3, estrogen can control the availability of ATP (from DPNH oxidation) as well as fatty acid or steroid synthesis (through TPNH formation) thus accounting for the characteristic anabolic and lipogenic effects.

CONCLUSION

Insulin influences fatty acid metabolism primarily by effecting neutral fat synthesis; GH, ACTH, TSH, epinephrine, and glucagon favour FFA

release from adipose tissue into the liver; whereas estrogens and thyroxine effects on fat metabolism are exerted through control of TPNH production. A generalised scheme of the influence of hormones on lipid metabolism may be represented thus (Langdon, 1960)



Ketosis and increased fatty acid oxidation are caused by overloading of the liver by FFA from extrahepatic tissues. Glucose, by providing α -glycerophosphate for the esterification of FFA, and insulin, by inhibiting the release of FFA from adipose tissue, reduce ketogenesis. Though many specific enzymes have been reported to be increased or decreased in diabetes, it is doubtful whether insulin directly influences any enzymes in the metabolism of lipids. It is likely that most hormonal effects on lipid metabolism are exerted by control of lipolysis in the adipose tissue or control of synthesis of cofactors like TPNH or cyclic AMP.

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