Review Letter

SHORT-TERM HORMONAL CONTROL OF HEPATIC CARBOHYDRATE AND LIPID CATABOLISM

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1. Introduction

The aim of this article is to highlight the existence of a range of hormones which can exert rapid catabolic effects on the liver. Several of these hormones do not appear to act via cyclic-AMP, whereas cations may be implicated in the response mechanisms. For comparison, facets of the more well-established actions of glucagon and adrenaline will be mentioned. An underlying purpose is to consider the functional significance of hepatic metabolic processes in adaptive and pathological states, as only in this way can the importance of hormonal effects be judged. As a prelude to this and the other objectives, the preferred blood-borne precursors for hepatic biosynthesis will be reviewed. A disclaimer must be entered against the possibility of comprehensive coverage here of relevant published articles. There are too many excellent papers, to permit such coverage. Instead, a selective and somewhat personalised approach is adopted.

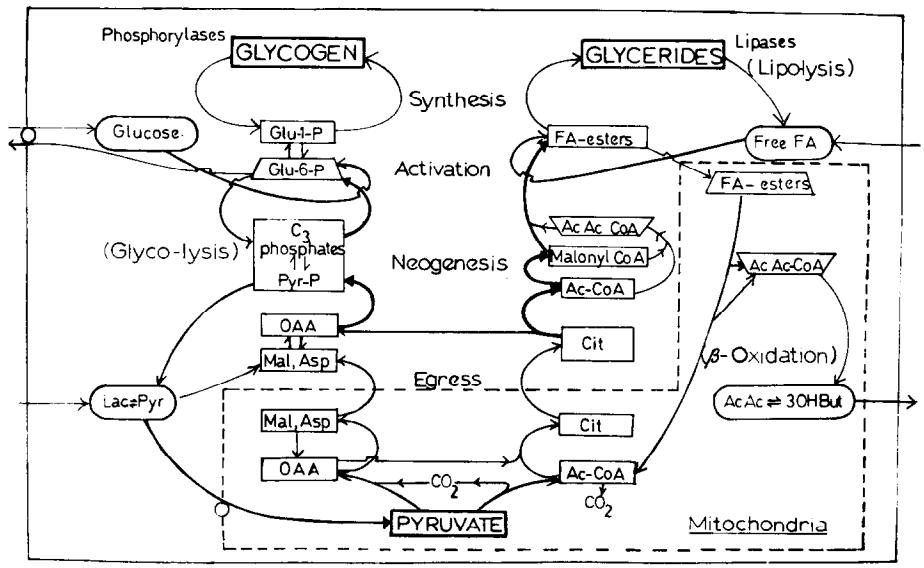
2. Glycogen and glycerides: formation and fate

A major locus of short-term hormone action on the liver is on the metabolism of the main fuel stores in the tissue viz. glycogen and glycerides. We may recapitulate some common features in the metabolism and function of these molecules (scheme 1). Both can be rapidly synthesised de novo ('neogenesis') from simple metabolites in the carbohydrate/amino acid pool; thus in pathway terms, gluconeogenesis is to some extent analogous to fatty acid synthesis ('liponeogenesis'). Also, conversion of glucose-phosphates to glycogen is analogous to 'esterification' of fatty acyl esters to glycerides. Finally, both glycogen and glycerides can be degraded by pathways which supply acetyl units for combustion, support ATP turnover during conversion to acetyl units, and produce soluble partial degradation products (lactate plus pyruvate, and ketone bodies, respectively).

Lactate and pyruvate are major precursors of both glycogen and glycerides in the liver, via neogenesis of glucose and fatty acids. Scheme 1 illustrates the prime role of pyruvate in the synthesis of these key storage molecules. An experimental basis for this view has come mainly from studies with the perfused liver. Thus in starved rats, synthesis of glycogen in response to ingested glucose does not involve blood-borne glucose as a carbon source, but rather a continuation of gluconeogenesis, hexose-phosphate products being directed to glycogen by the stimulatory role of glucose [1]. In perfused livers from fed animals, blood-borne glucose is also a good carbon-source for synthesised glycogen [2]; this has also been shown in cell suspensions [3].

In perfused liver of fed mice [4], or rat hepatocyte suspensions [5] lactate is preferred to glucose as a precursor of synthesised fatty acids. The lack of a major role of blood-borne glucose in providing carbon for fatty acids synthesised in the liver has been confirmed in intact mice [6] or rats (table II of ref. [7]).

An overall implication of these observations is that the fate of blood-borne lactate in liver can involve rapid conversion to both glucose and fatty acid (as well as to carbon dioxide). The balance between these fates depends on the control of the initial reactions of intra-mitochondrial pyruvate, thus emphasising the



Scheme 1. Inter-relationships and similarities in liver between the metabolism of glucose and fatty acids. Some major pathways currently thought to operate in the metabolism of glucose and fatty acids in liver parenchymal cells are shown in a simplified scheme. Analogies between the synthesis de novo of glucose and fatty acids from pyruvate (or, e.g., lactate) are highlighted. Where the boxes (pools) are in the same horizontal position on the diagram, or have a similar shape, this indicates equivalence of metabolic function. *Abbreviations:* Glu, Glucose; Pyr, Pyruvate; Lac, Lactate; Cit, Citrate; Mal, Malate; OAA, Oxaloacetate; Asp, Aspartate; AcAc, Acetoacetate; 3-OH-but, 3-hydroxybutyrate; FA, fatty acids; CoA, coenzyme A; P, Phosphate. Neogenesis of glucose or fatty acids is highlighted by a thick line; otherwise there are no implications about the relative predominance of pathways, which will alter depending on the state of the animal. The broken line indicates the mitochondrial membrane.

importance of the permease which carries pyruvate into mitochondria [8,9].

Turning to glycogen breakdown, this process has its major role in releasing glucose to blood, but can also supply acetyl units for fatty acid synthesis [4], presumably at times when there is net glycogen breakdown rather than synthesis. Indeed, this could constitute the main role of hepatic glycolysis [10] (since blood-borne glucose does not significantly enter this 'pathway'), although a role in providing acetyl units for oxidation to CO_2 also seems probable.

The degradation of glycogen and glycerides, to glucose 1-phosphate and free fatty acids plus glycerol, respectively, is shown in scheme 1. A great deal is already known about the control of hepatic glycogen breakdown [11] whereas very little is known about the control of hepatic glyceride degradation.

The close and to some extent reciprocal relationships in liver between glucose and fatty acid metabolism may be understood in the light of the major role of these processes in the rapid events of homeostasis of vital blood fuels, and in the adaptive hepatic responses to variations in ingested food. These adaptations (e.g., to starvation) involving reciprocal changes in neogenesis of fatty acids and glucose, may partly be viewed in terms of alteration of the fate of mitochondrial pyruvate. It is likely that, in animals ingesting significant quantities of glucose a major fate of plasma lactate is conversion to fatty acids. Such carbon cannot re-enter the carbohydrate pool, i.e., the Cori 'cycle' is thereby broken. During relative glucose deprivation, blood lactate is likely to convert predominantly to glucose, rather than fatty acid.

Given the above considerations, it is not surprising that some hormones seem to exert their most potent rapid effects simultaneously on carbohydrate and lipid metabolism in liver. Catabolic effects of this type are the subject of this article.

3. Short-term catabolic hormonal control of liver glycogen metabolism

Glycogen degradation can be rapidly stimulated by hormones. The paradigm for this type of effect is that of glucagon, the peptide produced by the A-cells of the endocrine pancreas, which enters the blood stream in the hepatic portal vein. Glucagon causes breakdown of liver glycogen at plasma concentrations of 10^{-11} M or greater, as may easily be demonstrated by measurements of glucose output in the perfused liver [12,13]. This remains one of the most sensitive and reproducible among metabolic effects of hormones (on any tissue).

Another well established catabolic hormone effect is that of adrenaline, which can stimulate liver glycogen breakdown at plasma concentrations of 10^{-8} M or greater [14]. Noradrenaline probably exerts a similar effect, over approximately the same concentration range.

A third hormone which stimulates the degradation of liver glycogen is vasopressin, the nonapeptide (counting cys-S-S-cys as two amino acids) produced by the posterior pituitary gland. In the perfused liver of the fed rat [14,15] or mouse [16] vasopressin can cause glucose release at concentrations of about 2.5×10^{-10} M.

Angiotensin II can also stimulate glycogen breakdown, as shown by measurements of glucose output in the perfused rat liver [14]; the minimum effective concentration is about 3×10^{-10} M.

Clearly a wide range of hormones is capable of stimulating glycogen breakdown in the liver (fig.1). This susceptibility to degradation is reminiscent of the response of adipose tissue triglyceride to a variety of hormones. Further hormones which can directly stimulate hepatic glycogen breakdown include parathyroid hormone [17] and some gut peptides, such as enteroglucagon and vasoactive intestinal peptide.

The converse process to glycogen breakdown is glycogen synthesis. Net synthesis of glycogen can be followed in the perfused liver, or in hepatocyte suspensions, from starved rats. Maximum rates require glucogenic sources of carbon which form glucose-phosphates, and also glucose to act as a stimulator of glycogen synthesis [1], i.e., glucose directs the newly-synthesised hexose-phosphates to glycogen ([1] for review see ref. [11]).

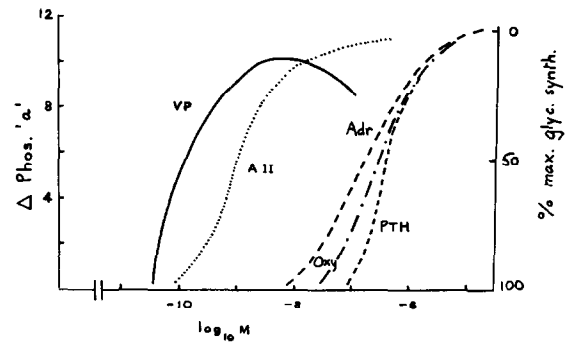


Fig.1. Concentration-dependence of short-term catabolic effects of hormones on liver glycogen metabolism. Livers were perfused with bicarbonate-buffered saline containing glucose and erythrocytes. Increase in the amount of glycogen phosphorylase *a* activity (Δ phos. *a* on ordinate: μmol/min/g) was determined 5 min after vasopressin (VP), angiotensin II (A II) or adrenaline (Adr); data, with permission, are from ref. [14]. In livers from starved rats, inhibition in the rate of net glycogen synthesis during 30 min. perfusion (% max. glyc. synth. on ordinate) was measured in response to oxytocin (oxy) or parathyroid hormone (PTH); data, with permission, are from refs. [18] and [19] respectively.

All of the hormones mentioned above can inhibit glycogen synthesis. The minimum effective concentration of vasopressin, which inhibits synthesis in the perfused rat liver, is about 10^{-10} M, i.e., the liver in this situation exhibits a more than 2-fold increase in sensitivity to hormone (cf. with the fed state) [15]. In view of this feature, the starved animal was selected for a study of the response of net hepatic glycogen synthesis to oxytocin and parathyroid hormone. Minimum effective inhibitory concentrations were respectively, about 2×10^{-8} M [18] and 5×10^{-8} M [19].

The concentration-dependences of some of these catabolic hormonal effects on glycogen metabolism in liver are shown in fig.1.

Regarding glycogen synthesis, no credible short-term stimulation of this process by any hormone acting alone and directly on the liver has yet been reported. Insulin has been tested many times for such an effect, but it appears that in fully aerobic conditions, insulin may not produce any rapid effect on hepatic glycogen metabolism (e.g. [2,20,21]). Insulin can however, suppress the actions of glucagon or adrenaline to stimulate glycogen breakdown [13]

and would presumably de-inhibit (i.e., stimulate) glycogen synthesis, in the presence of these hormones.

The process of gluconeogenesis is closely involved with events of glycogen metabolism (scheme 1; ref. [1]). So far, it has appeared that hormones which stimulate glycogen breakdown also stimulate glucose synthesis from a variety of precursors. Such stimulation has been shown for glucagon, adrenaline [22,23] and vasopressin [15] in experiments with livers from starved animals. Hence the overall effect of these hormones has been thought to be the promotion of glucose release by the liver, from both glycogen and glucogenic sources.

However, there is doubt about this general inference, in the case of adrenaline, vasopressin and angiotensin II, which at their lowest effective concentrations can all rapidly stimulate the amount of phosphorylase *a* in liver without associated glucose release [14]. These hormones may therefore (in the short-term in glycogen-containing livers at least), stimulate glycogenolysis to produce hexosephosphates for consumption within the liver, e.g., via glycolysis.

4. Short-term catabolic hormonal control of hepatic lipid metabolism

Hepatic glyceride metabolism has some general features in common with glycogen metabolism (scheme 1), although fat in liver (3–8% in normal animals, with triglyceride amounting to 1–3%) does not undergo such wide or rapid fluctuations as glycogen in respect of its role as a fuel store.

The processes of glyceride metabolism may be considered in the same order as were those of glycogen metabolism. Taking glyceride breakdown ('lipolysis') first, this process is difficult to measure in liver. Two valid measures would be (a) direct, i.e., net changes in glycerides with time, (b) changes in a relevant lipase activity. (In the case of glycogen, both these measures of degradation are easily available.) However, given this view, there are few systematic studies of hormonal stimulation of lipolysis which may be cited. Measurements of content of metabolites such as free fatty acids or their thioesters can in no way provide an estimate of lipolysis.

Glucagon can increase the extent of depletion of hepatic triglyceride during perfusion of the rat liver [24]; evidence of stimulation of lipolysis also comes from a study of release of ^{14}C-labelled free fatty acid from pre-labelled triglyceride during liver perfusion [25]. It would be expected that insulin would counteract this effect; indeed insulin alone can suppress triglyceride degradation in the perfused mouse liver [26].

Triglyceride synthesis from blood-borne free fatty acids can be stimulated by insulin [27] and probably inhibited by glucagon. Triglyceride export by liver, in very-low density lipoproteins, can be stimulated by insulin [27] and inhibited by glucagon [28].

The process of synthesis de novo of fatty acids (designated neogenesis of fatty acid in scheme 1), bears the same relationship to glyceride metabolism as does gluconeogenesis to glycogen metabolism (scheme 1). Again, we should look for rapid effects of catabolic hormones, which might be expected to inhibit fatty acid synthesis, as this is conventionally regarded as a 'biosynthesis' (in contrast to gluconeogenesis). This perhaps arbitrary distinction is unfounded in that hepatic liponeogenesis is faster than was hitherto believed, as may be shown by measuring ^{3}H incorporation from $^{3}H_2O$ [4,6]. But sure enough, vasopressin [16] adrenaline, and angiotensin II [29] can rapidly inhibit fatty acid synthesis, at least in mouse liver (table 1). In the case of vasopressin, the concentration-dependence of the inhibition of fatty acid synthesis is identical to that for stimulation of glycogen breakdown [16], suggesting that the initial stages of the mechanisms of action on these two processes may be common.

Glucagon can also inhibit fatty acid synthesis, but there may be a difference between this inhibition, and that exerted by other hormones. The inhibitory effect of glucagon in the perfused liver is not exerted at concentrations which occur in plasma (i.e. is less potent than that on glycogen breakdown: ref. 13), whereas there is inhibition in preparations such as slices where functional viability is not as good as it is in the perfused liver [30]. The inhibitory action of glucagon on fatty acid synthesis may be secondary in time to the primary metabolic effects of the hormone on carbohydrate metabolism. In particular, glucagon depletes the liver of glycogen, a favoured source of acetyl units for fatty acid synthesis [4].

Rapid effects of hormones on cholesterol synthesis in liver have not been studied as extensively as in the case of fatty acid synthesis. Glucagon can inhibit

Table 1
Inhibition of fatty acid synthesis in mouse liver by hormones

Hormone (M)	Fatty acid synthesis (μmol C_2-units/g/h)	Acetyl-CoA carboxylase activity (initial activity, as % of total)
None	27	56
Vasopressin, 3×10^{-9}	10	47
Adrenaline, 2×10^{-7}	12	37
Angiotensin II, 4×10^{-9}	8	42

Livers of fed mice were perfused with saline containing albumin, glucose (15 mM), lactate (10 mM) and erythrocytes. After addition of hormones, or in control livers, fatty acid synthesis was measured with ^3H_2O [16] and acetyl-CoA carboxylase activity was assayed, before and after 30 min treatment with citrate [29]. Data are taken, with permission, from refs. [16] and [29], (except for the vasopressin effect on acetyl-CoA carboxylase: unpublished experiments of G. Y. Ma and C. D. Gove). All hormone effects are significant (compared to the control value; $p < 0.05$), except that of vasopressin on the enzyme activity

synthesis of cholesterol in liver [31], whereas adrenaline may stimulate synthesis [32].

5. Mechanism of rapid catabolic action of hormones on hepatic glycogen

All hormones which can stimulate glycogenolysis act by increasing the amount of phosphorylase *a* in liver. This response, demonstrated for glucagon [33] adrenaline [14,22] angiotensin II [14,34] and vasopressin [7,14,35] must be mediated by alterations in the relative activities of phosphokinases and phosphatases which act on phosphorylase.

The action of glucagon on the liver appears to be mediated by the 'cascade' of responses initiated by the stimulation of the plasma membrane adenyl cyclase and followed by activation of cyclic-AMP-dependent protein kinase and phosphorylase *b* kinase, so that eventually phosphorylase *a* concentration increases. All the reactions of this cascade have been demonstrated to occur in intact-cell preparations in vitro, in response to glucagon [33,36,37].

There seems little reason to doubt this 'dogma' (a testimony to the most towering achievement in modern biochemical endocrinology, stemming, of course, from the work of E. W. Sutherland), in regard to glucagon action on the liver. Intriguingly though, cyclic-AMP may not be involved in the degradation of glycogen caused by the lowest effective concentrations of glucagon [38]; also, cations may be implicated in the mechanism of glucagon action, in conjunction with cyclic-AMP [39].

Apart from glucagon, hormones which can exert their short-term catabolic effect on the liver through cyclic-AMP include β-adrenergic agonists [40] and perhaps parathyroid hormone [17,41]. Whether this involves one cyclase and a series of hormone-binding subunits remains to be definitively clarified.

The other hormones which exert a catabolic effect on liver, mentioned above, do not act through cyclic-AMP. The existence of rapid catabolic effects in liver, not mediated by cyclic-AMP or its dependent protein kinase, was first shown for α-adrenergic agonists [40] and has been confirmed [22,23,36,37,42]. Although this is in one sense a 'negative' result, it is a very powerful one, as it suggests that *none* of the cellular effects of α-adrenergic agents are mediated by cyclic-AMP.

Vasopressin also does not increase the cyclic-AMP content of liver [43], and neither do angiotensin II or oxytocin (K. Siddle, C. Davies and D. A. Hems: unpublished data). The assayable protein kinase activity in hepatocyte suspensions is not increased by

vasopressin or angiotensin II [34,35]. An alternative candidate for mediation of the actions of these hormones on liver would be cyclic-GMP. However the content of this nucleotide in perfused liver does not alter in response to vasopressin, oxytocin or angiotensin II (K. Siddle, C. Davies and D. A. Hems: unpublished data). Cyclic-GMP has been shown to exert a catabolic action on liver glycogen [44] so that hypotheses which propose opposite effects ('Yin and Yang') of cyclic-GMP and cyclic-AMP in the short-term control of liver metabolism do not appear to be tenable, on the evidence so far. The role of cyclic-GMP in liver remains problematical.

Thus there is a group of hormones able to exert short-term catabolic effects on liver, which are not mediated by purine nucleotide cyclic monophosphates. This group of hormones comprises α-adrenergic agonists, vasopressin, oxytocin and angiotensin II (so far). There must be different receptors for catecholamines (α-receptors), neurohypopyseal peptides, and angiotensin II, as their structures are different. These receptors still have to be isolated and characterized.

Several of the above hormones are potent vasoconstrictor agents. In the rat liver, angiotensin II and adrenaline exert a direct potent constrictor action on the portal vasculature, whereas vasopressin does not [14]. These vasoconstrictor effects severely hamper the interpretation of catabolic effects obtained in vivo by hormone administration, since ischaemia and consequent hypoxia would themselves produce catabolic effects. However, it is established that the hormones under discussion here do not act solely on liver vasculature. In particular, they all can cause glycogen breakdown in hepatocyte suspensions, where there is no question of an ischaemic origin of the response [45–47].

How then may these hormones bring about the increase in amount of phosphorylase *a* in the liver? Inorganic ions, and Ca^{2+} in particular, are often implicated in the actions of extracellular agents on cells, so it is a reasonable hypothesis that Ca^{2+} is implicated in the actions of agents that do not affect purine nucleotide cyclic monophosphates. This seems to be the case for vasopressin action on hepatic glycogen breakdown, since extracellular Ca^{2+} is critical for this effect, to an extent that is more marked than for the actions of adrenaline and glucagon [45]. The same is true of angiotensin II action on hepatic glycogen breakdown [46,47].

As might be expected from the above observations, Ca^{2+} uptake by cells is increased by vasopressin and angiotensin II [46]. Ca^{2+} could be involved in the eventual increase in glycogen phosphorylase *a*, e.g., through activation of phosphorylase *b* kinase, which is very sensitive to Ca^{2+} [37,48,49]. However, the observation that extracellular Ca^{2+} is crucially implicated in hormone action is a far cry from solving the mechanism, especially in view of the fact that glucagon can also stimulate Ca^{2+} entry into liver, i.e., this response is not specific to hormones which do not affect the adenyl cyclase [46]. Thus the question of the mechanisms of action of this group of hormones which do not act via cyclic purine nucleotide monophosphates in liver is wide open.

6. Functional significance of catabolic hormone effects on the liver

The question arises of the importance in the animal of the above-described catabolic effects on the liver.

A common feature of these hormones is that they all increase in concentration in blood in stress, adaptive or pathological states. The role of glucagon in stress states has been widely documented and reviewed. Although glucagon in the hepatic portal vein undoubtedly can cause glycogenolysis in liver, over the 'normal range' of concentrations of hormone in plasma, glucagon may not be a major hormone in mature mammals. There are no common diseases involving excess or lack of glucagon. Administration of antibodies to glucagon produces no major upset [50]. Diabetes caused by pancreatectomy closely resembles that due to selective β-cell damage, showing that pancreatic glucagon action is not crucial in any of the features of diabetes (as yet reported), although there may be a contribution when raised plasma glucagon levels are present (for review, see ref. [51]).

Among the other hormones described here, adrenaline, vasopressin and angiotensin II are all potent vasoconstrictor agents in the intact animal. As would be expected, they have a role in the maintenance of blood pressure, especially in haemorrhagic states [52]. The circulating concentrations of adrenaline, vasopressin and angiotensin II also increase in

other conditions (e.g., starvation, hypoglycaemia, Na^+ depletion) to levels which will affect the liver (see discussion in ref. [14]).

A variety of stress states are associated with hyperglycaemia [53] perhaps to maintain the glucose content and osmolarity of the blood. It is probable that hormones such as those being discussed here have a role in producing this hyperglycaemia.

In the case of adrenaline, the view expressed here that circulating hormone can act directly on the liver to stimulate glycogenolysis merely resurrects an old idea, viz. that the antagonistic actions of insulin and adrenaline on liver glycogen are relevant in glucose homeostasis.

At their lowest effective concentrations, vasopressin, angiotensin II and adrenaline can stimulate glycogen degradation without associated glucose release [14]. Glucose-phosphates derived from glycogen may undergo further degradation by, e.g., glycolysis, in such conditions. This would make sense in hypoxic liver during shock.

If the hepatic catabolic effects of oxytocin and parathyroid hormone are relevant in vivo in any particular state of the animal, this state has not yet been identified.

Fatty acid synthesis in liver would be expected to decrease during stress, shock or adaptive states, as acetyl residues require to be conserved for oxidation. As one main precursor of fatty acid synthesised in liver is glycogen [4] such inhibition would free glycogen-derived glucose-phosphates for consumption in other pathways. The catabolic effect of hormones on fatty acid synthesis may be understood in this light.

In summary then, the range of catabolic hormone effects on liver contributes to the multiple rapid alterations required in states of stress, or adaptation. Many such hormone effects (on all tissues) then come into play, but recede in unstressed conditions. There does not appear to be such a wide battery of 'non-stress' hormones; thus 'non-stress' is merely a state where catabolic hormone effects are minimal.

7. Catabolic effects of hormones on liver in diabetes and obesity

The hormone effects on liver, which are the subject of this article, have relevance to the metabolic events in diabetes and obesity. Thus diabetes due to insulin deficiency is associated with hyperglycaemia, a relative depletion of liver glycogen (due partly to an intrinsic decline in hepatic capacity to synthesize glycogen: ref. [20]), an increase in capacity for gluconeogenesis, and a decline in hepatic fatty acid synthesis.

All these consequences would follow if the catabolic hormones under consideration here were to exert catabolic actions on liver in diabetes. When diabetes is of the severe ketotic type, there is hyperosmolarity associated with an increase in plasma renin activity [54] and presumably therefore of angiotensin II concentration. This increase could contribute to the hyperglycaemia and decline in hepatic fatty acid synthesis, through direct hepatic action. In such hyperosmolar diabetes, plasma vasopressin would also be likely to increase, and exert catabolic actions on liver; this possibility has not been systematically studied. Plasma adrenaline concentration can also increase in diabetes [55], so that this hormone may be a partial cause of hyperglycaemia in diabetes in some circumstances.

Obesity is a state in which intrinsic alterations in hormonal and metabolic status lead to a tendency to increase fat deposition in tissues (including blood vessels). Much information about this serious condition has come from the study of genetically obese rodents, in which the most significant alteration is perhaps their increased concentration of plasma insulin. In general, the alterations in lipid metabolism in obese rodents are less susceptible to reversal by food deprivation than are those in carbohydrate metabolism. This is true for example of the increases in hepatic lipogenesis [6], plasma turnover of triglyceride, free fatty acid and glycerol [56,57] and utilisation of plasma triglyceride by tissues [58] which are observed in genetically obese mice.

It is likely that some of these metabolic alterations in obesity are due to excessive influence of circulating insulin [59]. However, this explanation may leave several questions un-answered, such as why is insulin action not counteracted in tissues? This raises the general issue of hormonal responses in tissues of obese animals. One clue has emerged from studies with hormones which exert catabolic actions on liver. The liver in genetically obese mice is resistant to the inhi-

bition of lipogenesis which vasopressin causes in the liver of normal mice [60]. However, the liver is not resistant to the action of vasopressin to stimulate glycogen breakdown, or to the action of glucagon on glycogen breakdown.

It may be warranted to regard this lesion in vasopressin action on liver as reflecting very closely the inborn lesion in obese mice, as it is intractable to starvation, and as an impairment in inhibition of fatty acid synthesis would be expected to be associated with obesity. Therefore it appears that genetically obese mice, homozygous for the *ob* gene, exhibit a selective impairment in the cellular responses to extracellular effectors which are not mediated by purine nucleotide cyclic monophosphates. Such a defect in cell response mechanisms could cause alterations in the function of many tissues, such as are indeed exhibited by obese rodents. Extrapolating to human obesity, this inference would suggest that attention be directed to the rapid response mechanisms of cells, (to catabolic agents, neurotransmitters, etc.) which do not operate through purine nucleotide cyclic monophosphates, in order to gain insight into this condition, and to bring about therapeutic advances.

8. Conclusion

The above account has brought out the existence of a range of hormones which can exert catabolic effects on liver glycogen and fat metabolism. The hepatic effects of these hormones are relevant in the intact animal. Some of these hormones do not exert their actions through cyclic-monophosphates of adenosine or guanosine. Resolution of the mechanisms underlying their effects on liver cells should provide insight into regulatory responses in cell membranes, and perhaps into endocrine disorders.

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