Rapid hormonal control of hepatic catabolism in health and disease

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Introduction
There are lacunae in our insights into the effects of hormones on metabolic processes in the liver.

The aim of this article is to explore the role of hormones which produce direct rapid catabolic effects in stress or adaptive states. In particular, the role of catecholamines, vasopressin and angiotensin in shock, diabetes and obesity will be discussed.

Hormonal stimulation of catabolism in the normal liver
A range of hormones can exert catabolic effects on hepatic metabolism, as measured for example by the stimulation of glycogenolysis or inhibition of fatty acid synthesis (for review see Hems, 1977).

The hormones which exert catabolic effects on liver fall into two groups. (i) Those which act via cyclic-AMP, including glucagon, β-adrenoceptor stimuli, and perhaps parathyrin and peptides released by the gut. It is now widely accepted that the action of glucagon and β-adrenoceptor stimuli on liver is 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 (for reviews see e.g.: Exton & Park, 1972; Unger & Orci, 1976). (ii) Those which do not act via cyclic-AMP or cyclic-GMP but may act via redistribution of Ca²⁺ in cells, including α-adrenoceptor stimuli, vasopressin, oxytocin and angiotensin.

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 (Sherline, Lynch & Glinsmann, 1972), and this observation has been amply confirmed (e.g. Pointer, Butcher & Fain, 1976; Assimacopoulos-Jeannet, Blackmore & Exton, 1977; Birnbaum & Fain, 1977; Keppens, Vandenheede & De Wulf, 1977; Van de Werve, Hue & Hers, 1977).

Additional hormones which can exert a rapid potent stimulatory effect on hepatic glycogenolysis include vasopressin (Hems & Whitton, 1973; Hems, Rodrigues & Whitton, 1976, 1978c; Keppens et al., 1977; Van de Werve et al., 1977) and angiotensin (Hems et al., 1976, 1978c; Keppens & De Wulf, 1976; Keppens et al., 1977).

These hormones resemble α-adrenergic agonists in that their effects on liver are not mediated via cyclic-AMP or cyclic-GMP. Thus vasopressin does not increase the cyclic-AMP or cyclic-GMP content of liver, and neither does angiotensin nor oxytocin (Hems, Davies & Siddle, 1978a).

Catabolic-acting hormones also inhibit fatty acid synthesis in mouse liver (Ma & Hems, 1975; Ma, Gove & Hems, 1977, 1978), as do glucagon and cyclic-AMP in rat liver (e.g. Harris, 1975). They also can stimulate hepatic gluconeogenesis (for effects of vasopressin, angiotensin and oxytocin see Whitton, Rodrigues & Hems, 1978).

The concentration-dependence of some of these rapid direct catabolic effects on hepatic metabolism are shown in Fig. 1.

All hormones which stimulate hepatic glycogenolysis increase the quantity of available phosphorylase a in liver. Glucagon, adrenaline and vasopressin can activate hepatic phosphorylase in the intact animal (Hems, Whitton & Ma, 1975c).
Those hormones which can stimulate hepatic glycogenolysis (or gluconeogenesis), in a manner...
FIG. 1. Concentration-dependence of rapid catabolic effects of hormones on the liver

The concentration-dependence of effects of various hormones on liver are shown. The percentage scale represents the range from the minimum to the maximum effect exerted by each hormone. (a) Intra-hepatic effects: activation of glycogen phosphorylase in suspensions of rat hepatocytes (---: Keppens & De Wulf, 1976; Van de Werve et al., 1977; Hems et al., 1978c), or inhibition of fatty acid synthesis in perfused mouse liver (---: Ma & Hems, 1975; Ma et al., 1977).

(b) Stimulation of glucose release, in suspensions of hepatocytes from starved (---: Whitton et al., 1978) or fed (-----: Hems et al., 1978c) rats, or in perfused rat liver (---: Hems et al., 1976). Curves for glucagon effects are drawn from data from many published articles. Abbreviations: VP, [8-arginine]vasopressin; Ang, angiotensin; Adr, adrenaline; Gluc, glucagon.

not mediated by cyclic-AMP or cyclic-GMP, may exert their metabolic effects via modulation of Ca2+ movements in cells (Stubbs, Kirk & Hems, 1976; Keppens et al., 1977; Assimacopoulous-Jeannet et al., 1977; Van de Werve et al., 1977; Birnbaum & Fain, 1977; Foden & Randle, 1978; Hems et al., 1978c; Whitton et al., 1978; Blackmore, Brumley, Marks & Exton, 1978; Chen, Babcock & Lardy, 1978). Stimulation of phosphatidylinositol turnover (e.g. by vasopressin: Kirk, Verrinder & Hems, 1977, 1979) could be implicated in the control of Ca2+ distribution.

All the above-mentioned hormones can inhibit net glycogen synthesis. Further hormones which can exert this effect include parathyrin (Hems, Harmon & Whitton, 1975a) and oxytocin (Whitton & Hems, 1976). These effects appear to be less potent than those shown in Fig. 1, and their significance in vivo is not established.

The hepatic effects of the group of hormones which do not act via purine nucleoside cyclic monophosphates differ from those of glucagon in several ways. For example, vasopressin can activate pyruvate dehydrogenase in liver (Hems, McCormack & Denton, 1978b) and perhaps therefore activates glycolysis, and can also activate phosphatidylinositol turnover (Kirk et al., 1977, 1979). Glucagon does not appear to exert these effects. Thus a range of hormones which are implicated in the systemic events of acute stress (vasopressin, angiotensin, α-adrenergic receptor stimuli) can affect liver in a manner which is catabolic, but different from the effects of glucagon.

Another general point is that a wide range of molecules which can exert rapid catabolic effects on tissues (including liver) is emerging, whereas there appear to be fewer anabolic-acting (or anti-catabolic) hormones. Thus, in regard to the role of rapid effects of extracellular modifiers (e.g. hormones) in disease, it may be that catabolic states (e.g. diabetes, cachexia) ensue when there is an excess of such hormones (or tissue hypersensitivity), whereas anabolic states may merely imply a diminution (below 'normal') in the effects of the same cluster of hormones.

Hormone effects on liver in diabetes

Circulating concentrations of hormones with catabolic effects on the liver can be altered in diabetes (to an extent depending on severity, type, duration etc.). The significance of the increase in plasma concentration of glucagon in diabetes is well documented (for reviews see: Unger & Orci, 1976; Unger, Raskin, Srikant & Orci, 1977; Unger, Dobbs & Orci, 1978).

One may ask whether other hormones with catabolic effects on tissues could be implicated in the events of diabetes, e.g. in the hepatic glycolgenolysis, or decline in hepatic fatty acid synthesis characteristic of this condition. The concentration of catecholamines in plasma can be increased in acute ketoacidotic diabetes (Christensen, 1974; Robertson, Halter & Porte, 1976). Although this may not be generally true of diabetic patients, the role of the sympathetic nervous system and
circulating catecholamines in diabetes clearly merits further study.

The plasma vasopressin concentration would be expected to rise when there is hyperosmolarity, as occurs in many cases of acute insulin-deficient diabetes (coma), and indeed such an increase occurs (Zerbe, Vinicor & Robertson, 1978; V. P. Ang, H. M. Mather, T. R. E. Pilkington & J. S. Jenkins, personal communication).

Plasma renin activity has also been reported to increase in diabetic patients (Christlieb, Assal, Katsilambros, Williams, Kozak & Suzuki, 1975; Zerbe et al., 1978). A persistent increase in plasma angiotensin II is feasible in diabetes, as this hormone is continuously present in plasma at significant concentrations, whereas adrenaline and vasopressin exhibit different behaviour, only reaching their highest concentrations transiently during acute stress.

A simple way to assess the likely significance of hormones in diabetes is to compare the minimum effective concentration producing effects in liver with concentrations reported in plasma. This comparison is made in Table 1, where concentrations in plasma in diabetes are compared with the lowest concentrations which can activate phosphorylase in liver. Clearly, these concentrations are of the same order. Thus it seems likely that circulating catecholamines, vasopressin and angiotensin II can directly stimulate hepatic glycogenolysis in vivo, and thereby could contribute to the glycogen depletion and hyperglycaemia of diabetes, at least in severe acute ketoacidosis.

The question arises of the relevance of other rapid hepatic effects of catecholamines, vasopressin and angiotensin during diabetes. These hormones can potently inhibit hepatic fatty acid synthesis, and stimulate gluconeogenesis. Therefore, on the above-described basis, it is reasonable to suggest that these three hormones could contribute to these alterations in liver function during acute ketoacidotic diabetes.

**Hepatic catabolism in shock**

Circulatory shock is a state in which many adaptive responses are set in train. These include

### Table 1. Significance of hormone effects on liver

Minimum effective concentrations of hormones which activate glycogen phosphorylase in isolated liver preparations are compared with those present in plasma during haemorrhagic shock or acute ketoacidotic diabetes. The measurements quoted for shock or diabetes are all significantly increased relative to those in the matched controls. Values for hepatic responses are for rat liver, whereas those for haemorrhage are mainly from dogs and those for diabetes are from patients. Values have been rounded off, in view of the difficulties of documenting minimum effective concentrations, and the existence of inconsistencies (albeit minor) between measured plasma concentrations. The rat liver responses to glucagon and catecholamines are well established, and those (of phosphorylase) to the other hormones are described by Hems et al. (1976, 1978c). Some hepatic responses other than those of phosphorylase are shown in Fig. 1.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Minimum for activation of phosphorylase</th>
<th>Present in blood</th>
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<tbody>
<tr>
<td></td>
<td>Perfused Hepatocyte suspensions</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Glucagon</td>
<td>350</td>
<td>500 (Lindsey, Faloona &amp; Unger, 1975)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200,000</td>
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<tr>
<td>Catecholamines</td>
<td>2000</td>
<td>(Jakschik, Marshall, Kourik &amp; Needleman, 1974)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>40</td>
<td>50–2000 (Errington &amp; Rocha e Silva, 1972)</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>60</td>
<td>200–6000 (Hodge, Lowe &amp; Vane, 1966; Zakheim, Molteni, Mattioli &amp; Park, 1976)</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>—</td>
<td>130‡ (Poraling, Taverne &amp; Ellendorff, 1977)</td>
</tr>
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† Plasma renin activity, in ng of pro-angiotensin produced h⁻¹ ml⁻¹.
‡ During labour in miniature swine.
hormonal responses, as with trauma in general (Johnson, 1972). One of the most dramatic effects of acute haemorrhage is that there is an increase in the plasma concentration of hormones which are potent vasoconstrictors, such as catecholamines, vasopressin and angiotensin II (Table 1).

These hormones also exert a potent stimulation of hepatic glycogenolysis (Fig. 1), at concentrations of the same order as those observed in plasma during haemorrhagic shock (Table 1). Although the hormones exert constrictor effects on the hepatic vasculature (Richardson & Withington, 1976, 1977), their hepatic metabolic effects are not solely due to this action, as they can be observed in suspensions of isolated parenchymal cells (Fig. 1; Table 1).

Thus it appears that, in hypovolaemic states, a group of hormones are secreted into plasma to bring about vasoconstriction and hepatic glycogenolysis. The purposes of the glycogenolysis, and the resultant ‘stress hyperglycaemia’, include provision of glucose to sustain glycolysis in extrahepatic tissues during shock, and also to maintain osmolarity. A major proportion of the restored osmolarity during compensation for shock is due to plasma (and extracellular) glucose (Jarhult, Holmberg, Lundvall & Mellander, 1976). Hepatic glycogenolysis during shock may also supply internal carbon to the glycolysis pathway, to maintain ATP turnover.

The difference in mechanism of action between the two groups of catabolic-acting hormones which affect liver (those which act via cyclic-AMP, and those which do not) thus has a functional counterpart (the difference in vasoactive potency). It may be that hormones which serve a major catabolic role in acute stress do not act via purine nucleoside cyclic monophosphates, whereas hormones which do so act are involved in less acute dietary responses. Of course, non-dietary stress leads to starvation, so these adaptive responses would overlap. This view would accord with the ‘glucose deprivation’ role of cyclic-AMP in prokaryotes. Also, this subdivision into groups of catabolic-acting metabolic hormones could provide a basis for a speculation regarding the functions of tissue $\alpha$-adrenoceptors (acute stress) and $\beta$-adrenoceptors (nutritional and related less acute stresses).

**Resistance to hormonal control of hepatic catabolism in obesity**

It is regrettable that although obesity is the major nutritional disorder in the materially developed countries its nature has been misapprehended. Obesity may be defined as an absolute or relative increase in body fat, compared with that in average members of the relevant matched population. As a result of the efforts of Astwood, and others since, it is becoming more widely realised that obesity reflects an intrinsic alteration in biochemical make-up (just as does diabetes).

Advances in understanding of metabolic events have partly arisen from the use of animal models. There are several excellent models of obesity and diabetes (Herberg & Coleman, 1977). The realisation that obesity is an intrinsic endocrine disorder has come partly from the study of mutant obesity in rodents, which clearly involves an irreversible increase in the proportion of body fat, regardless of the nature or quantities of food intake.

In obesity, the hormonal control of catabolic processes in tissues might be expected to be altered in such a way as, for example, to diminish normal rates of lipolysis and to increase fatty acid synthesis. For example, in genetically obese rodents, there may be resistance to the lipolytic action of adrenaline in adipose tissue.

The liver of genetically obese (ob/ob) mice exhibits resistance to the inhibitory effects on fatty acid synthesis of glucagon (Ma et al., 1978), vasopressin (Hems & Ma, 1976) and adrenaline and angiotensin (Ma, Gove, Cawthorne & Hems, 1979). These impairments in catabolic hormone action are selective, as they occur in association with a normal glycogenolytic response to hormones.

The failure of vasopressin, angiotensin, adrenaline and glucagon to inhibit fatty acid synthesis in the liver of ob/ob mice constitutes the first evidence in genetically obese rodents of a failure of the process of fatty acid synthesis to respond normally to inhibitory hormones. This impairment is likely to reflect closely the inborn error in these animals, for three reasons: (1) it is not reversible by relatively severe food privation; (2) a lesion in the inhibitory control of fatty acid synthesis would be of direct pathogenic importance, as obesity is by definition a state in which there is excess deposition of fat; (3) in intact obese mice the increase in fatty acid synthesis is intractable to starvation (Hems, Rath & Verrinder, 1975b) as are other alterations in lipid metabolism (Hems, 1979). Such irreversibility suggests that the lesion in obese mice could reside in the control properties of lipid metabolism.

Therefore the genetic obesity in the ob/ob mouse could be a consequence of a defective response in cells (see also Chang, Huang & Cuatrecasas,
normal constraints, on fatty acid synthesis in particular. The observed defect does not involve the adenylate cyclase system, as vasopressin and angiotensin II do not act through this system in the liver (Hems et al., 1978a).

Resistance to catabolic-acting effectors in obesity could be directly relevant to the consequences of hyper-insulinemia. The development of the obesity could reflect a decline in catabolic regulatory effects in tissues which (in normal mice) over-ride insulin stimulation of tissues, keeping obesity in check.

As the mechanism of action of the above hormones (even glucagon) on hepatic fatty acid synthesis is not clear, the lesion in the liver of obese animals cannot be described in mechanistic terms.

The nature of insulin action on tissues is clearly of major significance in obesity. There is 'insulin-resistance' in many types of obesity, in the general sense that both insulin and glucose concentration may be high in plasma, implying that insulin is not as effective (at a given concentration) in clearing glucose from plasma, as in matched normal animals (or man).

Similarly, at the tissue level, insulin-resistance is often demonstrable in obesity, as a shift 'to the right' of the concentration-dependence of a given insulin effect on adipose tissue or muscle.

Insulin-resistance, assessed at the level of the whole animal, is especially marked in genetically obese rodents. It is partially reversible, which makes sense, as primary insulin-resistance would not be expected to lead to obesity.

Study of insulin-resistance at the level of liver as a direct target requires the existence of a credible insulin effect on a metabolic process, so that concentration-dependence of the insulin effect may be evaluated. Insulin effects on hepatic metabolism in vitro are notoriously small and inconsistent. One repeatable effect of insulin on liver in vitro is suppression of glucagon-induced glycogenolysis. In the perfused liver of genetically obese mice, resistance to insulin suppression of glucagon-induced glycogenolysis is manifest, but is reversed by partial starvation (Ma et al., 1978).

It remains probable that insights gained into the genetic obese syndromes in rodents will provide useful clues about the nature of obesity in human subjects. The above considerations suggest that attention be directed to the rapid response mechanisms of cells (to catabolic agents, neurotransmitters etc.), which do not operate through purine nucleoside cyclic monophosphates, in order to gain insight into this condition and to bring about therapeutic advances.

Conclusions
The above account, selectively based on the control of carbohydrate and lipid metabolism in liver, has been designed to show that a great deal remains to be clarified about the direct rapid catabolic effects of hormones on the liver, about the mechanisms that underlie these effects, and about the relevance of these effects in disease. It is likely that such information will yield insights into the pathogenesis of a range of disorders, and also possible that a greater opportunity for therapeutic intervention would thereby emerge.

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References


