

Regulation of hepatic fructose 2,6-bisphosphate concentrations and lipogenesis after re-feeding in euthyroid and hyperthyroid rats

A regulatory role for glycogenesis

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The time courses of restoration of fructose 2,6-bisphosphate (Fru-2,6- P_2) concentrations and rates of lipogenesis after chow re-feeding were correlated with glycogen concentrations and rates of glycogen synthesis in livers of 48 h-starved euthyroid and hyperthyroid rats. Although a regulatory function for glycogen in the regulation of Fru-2,6- P_2 concentrations was excluded, an inverse relationship between rates of glycogenesis and Fru-2,6- P_2 concentrations indicated a role for glycogenesis in the suppression of Fru-2,6- P_2 concentrations during the early (0–4 h) period of re-feeding. There was also a negative correlation between rates of glycogenesis and lipogenesis, and a positive correlation between glycogen concentrations and the lipogenic rate. Decreased rates of glycogenesis in hyperthyroid rats were associated with increased rates of lipogenesis. The response of Fru-2,6- P_2 to changes in the glycogenic rate was modified by hyperthyroidism, although a negative correlation was again observed.

INTRODUCTION

In starvation, hepatic carbon flux is directed towards glucose production via glycogenolysis and gluconeogenesis. There is net glucose production from non-carbohydrate precursors, such as glycerol and certain amino acids, in addition to recycling of glucose carbon via the Cori cycle. On re-feeding after starvation, glycogen deposition is observed. The synthesis of hepatic glycogen utilizes C_3 derivatives of glucose via the gluconeogenic pathway, flux through which continues to glucose 6-phosphate (reviewed by Katz & McGarry, 1984). The glucose 6-phosphate formed via gluconeogenesis is directed towards glycogen synthesis. During this period it is thought that glycolysis from hexose phosphates may be restricted by continued low concentrations of fructose 2,6-bisphosphate (Fru-2,6- P_2), a potent stimulator of 6-phosphofructo-1-kinase (Van Schaftingen *et al.*, 1981; Pilkis *et al.*, 1981; Uyeda *et al.*, 1981). Alternatively, there may be differential sensitivity of glycogenesis and glycolysis to glucose (Hue *et al.*, 1984).

Increases in Fru-2,6- P_2 are observed only after a threshold glycogen concentration has been achieved (Kuwajima *et al.*, 1984). There may also be a regulatory link between glycogen metabolism and lipogenesis. After re-feeding, lipogenic rates remain low (Agius & Williamson, 1981; Sugden *et al.*, 1982), but inhibition of glycogenesis at the level of phosphoenolpyruvate carboxykinase by 3-mercaptopyruvate leads to marked increases in lipogenesis (Sugden *et al.*, 1983b; Holness *et al.*, 1987a). The mechanism whereby lipogenesis is increased is unknown. However, it is possible that there is preferential utilization of oxaloacetate for glycogenesis rather than for citrate synthesis and lipogenesis. In addition, glycogen itself may be a regulator of lipogenesis.

It has been demonstrated *in vitro* that there is a positive correlation between the glycogen concentration and the rate of lipogenesis (Salmon *et al.*, 1974), but the means by which any stimulation of lipogenesis by glycogen may be achieved is unknown.

In the present work we have examined the relationship between rates of glycogen synthesis, Fru-2,6- P_2 concentrations and rates of lipogenesis. The aims of the study were to investigate the possible role of glycogenesis as a factor in the restriction of restoration of Fru-2,6- P_2 concentrations and lipogenic rates after re-feeding. We have investigated this relationship after chow re-feeding both of 48 h-starved euthyroid rats and of 48 h-starved rats treated with tri-iodothyronine (T_3). Experimental hyperthyroidism provides a model to probe the relationship between glycogenesis, Fru-2,6- P_2 and lipogenesis after re-feeding. Not only is glycogen synthesis impaired (Sugden *et al.*, 1981; Holness & Sugden, 1987a), but lipogenesis is increased (Sugden *et al.*, 1981, 1983a). Furthermore, hyperthyroidism increases lipogenic capacity (Diamant *et al.*, 1972; Kumar *et al.*, 1977) and, although reports have been conflicting, changes in the activity of one or more enzymes of glycogen metabolism (see, e.g., Preiksaitis & Kunos, 1979; Takahashi & Suzuki, 1979; Malbon & Campbell, 1984).

MATERIALS AND METHODS

Sources of materials were as in Sugden *et al.* (1983a,b). Standard laboratory chow was purchased from E. Dixon & Sons (Ware) Ltd., Ware, Herts., U.K., and contained 52% digestible carbohydrate.

Female albino Wistar rats (180–220 g) were starved for 48 h in grid-bottomed cages before use. Rats were made hyperthyroid by the subcutaneous injection of T_3 dissolved in 10 mM-NaOH/0.03% bovine serum albumin

Abbreviations used: Fru-2,6- P_2 , fructose 2,6-bisphosphate; T_3 , tri-iodothyronine.

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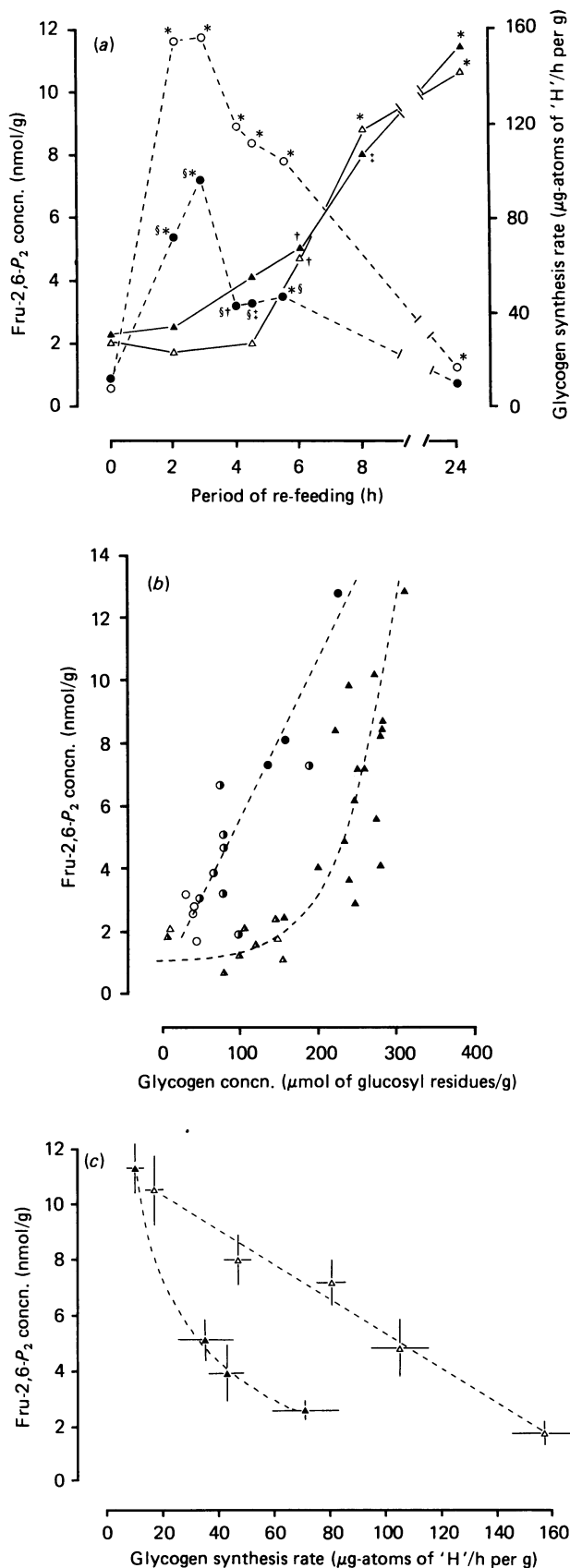


Fig. 1. Relationships between fructose 2,6-bisphosphate, glycogen and glycogenesis after re-feeding in euthyroid or hyperthyroid rats

(a) Rates of glycogenesis (○, ●) and concentrations of Fru-2,6-P₂ (△, ▲) in livers of previously starved euthyroid

(100 μg/100 g body wt. per day) for 3 consecutive days, being starved during the initial 2 days of treatment and re-fed on day 3. Control rats were injected with an equivalent amount of solvent. Experiments were started between 08:30 and 09:30 h, when chow was provided *ad libitum*. Rats were sampled at intervals from 1 h to 24 h after the provision of chow. Chow intakes during each period were not significantly affected by T₃ treatment (results not shown).

Rates of lipogenesis were estimated as ³H incorporation from ³H₂O into tissue saponifiable fatty acid (Stansbie *et al.*, 1976). Rates of glycogen synthesis were estimated in the same livers by the incorporation of ³H from ³H₂O into glycogen (Postle & Bloxham, 1980). ³H₂O was administered by intraperitoneal injection at 1 h before sampling (see Holness *et al.*, 1987b, for details). Rats were dissected while under pentobarbital anaesthesia (5 min; 6 mg/100 g body wt.).

Glucose concentrations were determined in KOH-neutralized HClO₄ extracts of blood sampled from the hepatic portal and the hepatic veins. Glycogen concentrations were determined in extracts of freeze-clamped livers. Details of these methods are given in Bergmeyer (1974). Fru-2,6-P₂ concentrations were measured in extracts of freeze-clamped livers by activation of 6-phosphofructo-1-kinase as described by Richards & Uyeda (1980), after extraction as described by Hue *et al.* (1982). Concentrations and rates are expressed per g wet wt.

Statistical significance of effects of chow re-feeding and hyperthyroidism was assessed by Student's unpaired *t* test. Results are given as means ± S.E.M. for the numbers of rats indicated.

RESULTS AND DISCUSSION

Glycogen concentrations after chow re-feeding

Starvation for 48 h is associated with depletion of hepatic glycogen. The provision of chow to previously starved euthyroid rats leads to glycogen synthesis (Fig. 1a) and deposition (Holness & Sugden, 1987a). The most rapid increases in glycogen concentrations are observed over the first 4 h (Holness & Sugden, 1987a). These increases correlate with high rates of glycogenesis, estimated by the incorporation of ³H from ³H₂O into glycogen (Fig. 1a). Although some hepatic glycogen repletion is observed in hyperthyroid rats after the provision of chow, glycogen concentrations are lower than those of the euthyroid controls (Holness & Sugden,

(○, △) or hyperthyroid (●, ▲) rats at intervals after chow re-feeding. Values are means for 3–10 rats. Error bars are omitted for clarity. Statistically significant effects of chow re-feeding are indicated by †*P* < 0.05, ‡*P* < 0.01, **P* < 0.001, and of hyperthyroidism by §*P* < 0.01. (b) Relationship between the concentrations of glycogen and Fru-2,6-P₂ in livers of previously starved euthyroid (△, ▲) or hyperthyroid (○, ●) rats after chow re-feeding. Rats were sampled at 0–2 h (△, ○), 2–5 h (▲, ●) or 5–24 h (▲, ●) after the provision of chow *ad libitum*. (c) Relationship between the rate of glycogenesis and Fru-2,6-P₂ concentrations in livers of previously starved euthyroid (△) or hyperthyroid (▲) rats after chow re-feeding. The values shown are means of values obtained for euthyroid rats sampled at 2, 4, 6, 8 or 24 h after chow re-feeding, and for hyperthyroid rats sampled at 2, 4, 6 and 24 h after chow re-feeding.

1987a) and rates of ^3H incorporation into glycogen are also decreased (Fig. 1a). Hyperthyroidism exerts its effects on glycogen repletion at site(s) distal to hexose phosphate formation (Holness & Sugden, 1987a). However, from these and the present results it is not possible to assess whether glycogen synthesis is impaired, or whether newly synthesized glycogen is degraded.

Response of Fru-2,6- P_2 to chow re-feeding

The time course of the response of hepatic Fru-2,6- P_2 to chow re-feeding is shown in Fig. 1(a). As observed by Kuwajima *et al.* (1984), increases in Fru-2,6- P_2 in livers of euthyroid rats were observed only after a lag period. The times at which increases in Fru-2,6- P_2 are observed have been suggested to be related to the deposition of a critical concentration of glycogen (Kuwajima *et al.*, 1984), and in the present experiments the relationship between the concentrations of Fru-2,6- P_2 and glycogen closely resembled that obtained by Kuwajima *et al.* (1984). Fru-2,6- P_2 concentrations remained low until that of glycogen exceeded approx. 200 μmol of glucosyl units/g. Subsequently, small increments in glycogen concentrations were associated with marked increases in Fru-2,6- P_2 concentrations (Fig. 1b).

The time course of restoration of Fru-2,6- P_2 concentrations in hyperthyroid rats was similar to that observed in euthyroid rats (Fig. 1a), even though glycogen deposition was impaired (Table 1). There was no indication that it was necessary to exceed a critical glycogen concentration before an increase in Fru-2,6- P_2 could be observed (Fig. 1b). It may be concluded either that any relationship between glycogen and Fru-2,6- P_2 concentration is fortuitous or that hyperthyroidism abolishes any requirement of Fru-2,6- P_2 synthesis for prior repletion of glycogen.

These results raise questions as to the mechanism whereby hepatic Fru-2,6- P_2 concentrations are maintained at low values for at least 4 h after chow re-feeding in euthyroid rats, and the way in which these mechanisms are affected by hyperthyroidism.

In Fig. 1(c) Fru-2,6- P_2 concentration is plotted as a function of the rate of glycogen synthesis. The inverse relationship observed in euthyroid rats suggests that a high rate of glycogenesis precludes an increase in Fru-2,6- P_2 . It is envisaged that the utilization of hexose phosphate as a result of activation of glycogen synthase (reviewed by Hers, 1976) limits the activity of 6-phosphofructo-2-kinase via a limitation of precursor supply. At later times, when glycogen repletion is largely complete, a high glycogen concentration may inhibit glycogen synthase phosphatase activity, thereby decreasing that of glycogen synthase (see De Wulf & Hers, 1968) to an extent sufficient to permit the accumulation of hexose phosphate and allow the formation of Fru-2,6- P_2 . A good correlation between hexose phosphate and Fru-2,6- P_2 concentrations has been demonstrated in isolated hepatocytes (Hue *et al.*, 1981). A decrease in glucose 6-phosphate (Newgard *et al.*, 1984) and a delayed increase in fructose 6-phosphate (Claus *et al.*, 1984) have been reported after carbohydrate re-feeding.

The failure to observe hexose phosphate accumulation in the early period after re-feeding suggests that glycogen synthase activity exceeds or is equal to the rate of glucose 6-phosphate supply. Decreased concentrations of glucokinase in starvation may limit the provision of glucose

6-phosphate via glucose phosphorylation, although net glucose uptake by the liver is observed (see below, and Holness & Sugden, 1987a,b). The failure of Kuwajima *et al.* (1986) to obtain a correlation between increases in Fru-2,6- P_2 and fructose 6-phosphate concentrations after sucrose administration presumably arises because, at the earliest sampling point (0.5 h), both fructose 6-phosphate and Fru-2,6- P_2 concentrations were already elevated.

In hyperthyroid rats, rates of hepatic glycogenesis were significantly lower than those observed in euthyroid rats (Fig. 1a). As it has been demonstrated that gluconeogenic flux from triose phosphate is not diminished in hyperthyroidism (Holness & Sugden, 1987a), it would be predicted that the accumulation of hexose phosphate (and thus of Fru-2,6- P_2) would be enhanced, particularly as glucokinase activity is restored more rapidly in response to re-feeding in hyperthyroid rats (Minderop *et al.*, 1987). There was a slight indication that increases in Fru-2,6- P_2 could be achieved more rapidly after chow re-feeding in hyperthyroid rats (Fig. 1a). Nevertheless, although Fru-2,6- P_2 concentrations were comparable with those found in euthyroid rats, they were inappropriately low for the rate of glycogenesis (Fig. 1c). Although this result could be explained by a specific effect of hyperthyroidism on 6-phosphofructo-2-kinase, we consider that it is more likely that there is increased removal of hexose phosphate via the pentose phosphate pathway and/or glucose-6-phosphatase. The concentrations of glucose-6-phosphate dehydrogenase and glucose-6-phosphatase are increased in livers of hyperthyroid rats (Maley, 1957; Tata *et al.*, 1963; Szepesi & Freedland, 1969). Increased rates of NADPH utilization via lipogenesis may permit increased flux through the pentose phosphate pathway. Moreover, measurements of portal-hepato-venous glucose concentration differences [P-V] after the administration of carbohydrate indicate inadequate suppression of hepatic glucose output in hyperthyroid rats (Holness & Sugden, 1987a,b). Although a positive value of [P-V] was observed after chow re-feeding, it was decreased relative to that found in the euthyroid controls (values of $+0.49 \pm 0.23$ mM and $+1.57 \pm 0.23$ mM, $P < 0.01$; means of measurements made from 0-4 h after the provision of chow), suggesting decreased net glucose uptake and phosphorylation.

Table 1. Hepatic lipogenic rates in 48 h-starved or chow-re-fed euthyroid and hyperthyroid rats

For experimental details see the text. Results are means \pm s.e.m. for 4-15 rats. Statistically significant effects of chow re-feeding are indicated by * $P < 0.01$; ** $P < 0.001$, and of T_3 treatment by † $P < 0.01$; †† $P < 0.001$.

| Nutritional status | Period of re-feeding (h) | Hepatic lipogenic rate (μg -atoms of ^3H /h per g wet wt.) | |
|--------------------|--------------------------|---|---------------------|
| | | Control | T_3 -treated |
| 48 h-starved | — | 3.4 ± 0.4 | 10.7 ± 1.0 †† |
| Chow re-fed | 2 | 8.6 ± 0.9 ** | 32.0 ± 5.0 **†† |
| | 4 | 15.0 ± 1.9 ** | 30.1 ± 5.7 *† |
| | 6 | 31.4 ± 5.0 ** | 51.1 ± 11.6 * |
| | 24 | 45.6 ± 3.4 ** | 78.5 ± 4.8 **†† |

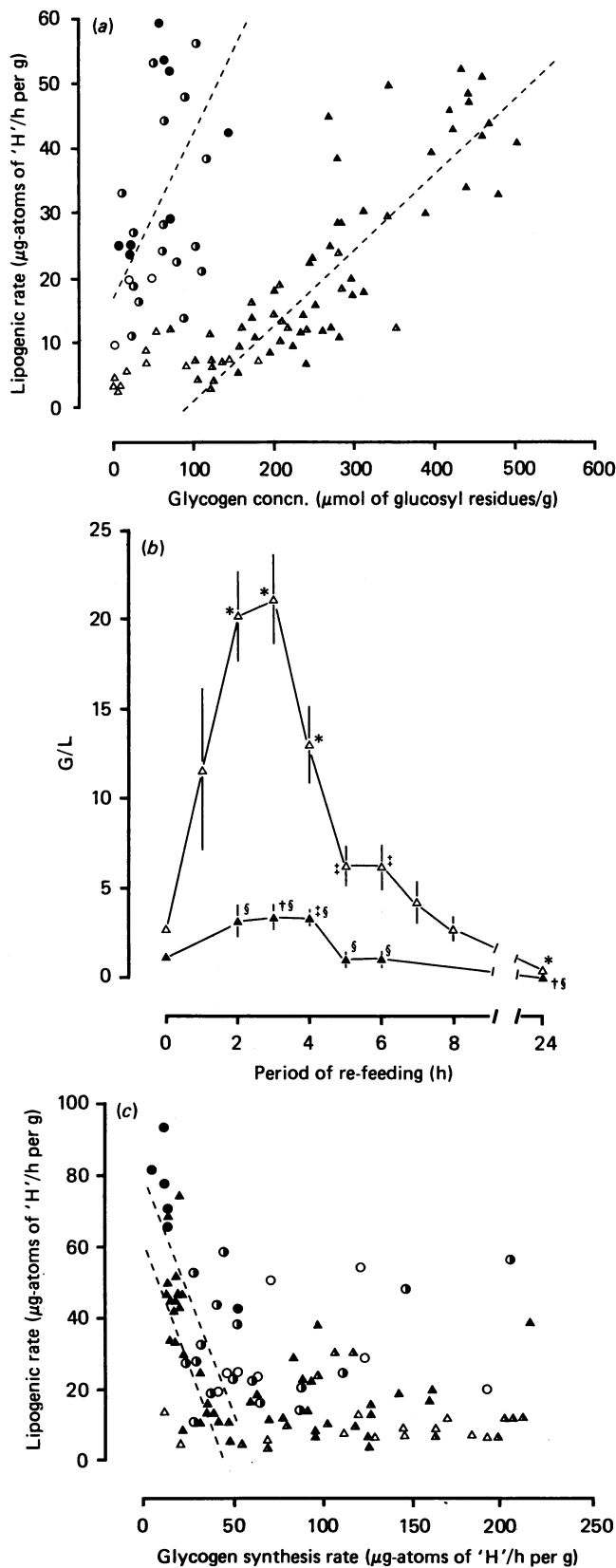


Fig. 2. Relationships between lipogenesis, glycogen and glyco-genesis in euthyroid or hyperthyroid rats

(a) Relationship between the glycogen concentration and rates of lipogenesis in livers of previously starved euthyroid (Δ , \blacktriangle , \blacktriangle) or hyperthyroid (\circ , \bullet , \bullet) rats after chow re-feeding. Rats were sampled at 0–2 h (Δ , \circ), 2–5 h (\blacktriangle , \bullet) or 5–24 h (\blacktriangle , \bullet) after the provision of chow

Time course of hepatic fatty acid synthesis after chow re-feeding

Starvation decreases hepatic lipogenesis in both euthyroid and hyperthyroid rats (Sugden *et al.*, 1981), but the administration of a glucose load to starved rats only increases lipogenesis if they have been made hyperthyroid (Sugden *et al.*, 1981, 1983a). However, if glycogen synthesis is blocked at the level of phosphoenolpyruvate carboxykinase, lipogenesis can be stimulated even in the euthyroid state (Sugden *et al.*, 1983b). This suggests a control site for both glycogenesis and lipogenesis at the level of oxaloacetate disposal. Stimulation of hepatic lipogenesis was observed within 2 h of the administration of chow, even in the euthyroid state (Table 1). This may suggest increased availability of oxaloacetate after chow, as opposed to glucose, re-feeding.

Both basal (starved) rates of lipogenesis and the lipogenic response to the provision of chow were affected by hyperthyroidism (Table 1). The basal rate of lipogenesis was increased by 215%, indicative of an increased lipogenic capacity (Diamant *et al.*, 1972; Kumar *et al.*, 1977). Differences were maintained after re-feeding. The increase in lipogenesis observed at 2 h after the provision of chow was greater than that found in euthyroid rats (200% versus 153%). Whereas in euthyroid rats the increases in lipogenic rate were gradual, this was not the case in hyperthyroidism, where restoration of the rate of lipogenesis to 40% of the 24 h-re-fed value had already been achieved within 2 h (Table 1).

Relationship between glycogen concentration and lipogenesis after chow re-feeding

On the basis of a positive correlation between glycogen content and rates of fatty acid synthesis in perfused liver, Salmon *et al.* (1974) proposed that a high glycogen concentration might stimulate the rate of fatty acid

ad libitum. In euthyroid rats there was no correlation between the glycogen concentration and the rate of lipogenesis at concentrations of less than 100 μmol of glucosyl residues/g ($r = 0.37$). In hyperthyroid rats there was a positive correlation over this concentration range ($r = 0.64$; line equation, $y = 0.03x + 17.0$). There was a positive correlation between the glycogen concentration and the rate of lipogenesis in euthyroid rats at concentrations above 100 μmol of glucosyl residues/g ($r = 0.85$; line equation, $y = 0.01x - 11.1$). (b) Ratio of the rate of glycogenesis (G) to the rate of lipogenesis (L) in livers of previously starved euthyroid (Δ) or hyperthyroid (\blacktriangle) rats at intervals after chow re-feeding. Rates of glycogenesis and lipogenesis were measured as ^3H incorporation from $^3\text{H}_2\text{O}$ into product in the same livers. Values are means for 3–15 rats. Statistically significant effects of chow re-feeding are indicated by † $P < 0.05$, ‡ $P < 0.01$, * $P < 0.001$, and of hyperthyroidism by § $P < 0.01$. (c) Relationship between the rate of glycogen synthesis and the rate of lipogenesis in livers of previously starved euthyroid (Δ , \blacktriangle) or hyperthyroid (\circ , \bullet , \bullet) rats after chow re-feeding. Rats were sampled at 0–2 h (\circ , Δ), 2–5 h (\bullet , \blacktriangle) or 5–24 h (\blacktriangle , \bullet) after the provision of chow *ad libitum*. There was a linear correlation between rates of glycogenesis and rates of lipogenesis at glycogenic rates of less than 50 $\mu\text{g-atoms}$ of $^3\text{H/h per g}$. Linear regression analysis gave a line equation of $y = -1.2x + 59.1$ ($r = 0.64$) for euthyroid rats, and a line equation of $y = -1.2x + 78.5$ ($r = 0.67$) for hyperthyroid rats.

synthesis. The dependence of lipogenesis on glycogen concentrations *in vivo* after chow re-feeding is shown in Fig. 2(a). At low concentrations (0–100 μmol of glucosyl units/g) there was no correlation between glycogen concentration and the rate of lipogenesis in euthyroid rats. At higher concentrations (100–500 μmol of glucosyl units/g), there was a positive correlation ($P < 0.001$) between glycogen concentration and the rate of lipogenesis. This latter range of glycogen concentrations is observed after approx. 3 h of re-feeding (the glycogen concentration at 3 h after the provision of chow was 132 ± 22 μmol of glucosyl units/g).

It could be argued that, as with Fru-2,6- P_2 , any relationship between lipogenesis and the glycogen concentration is fortuitous. Indeed, the high rates of lipogenesis in hyperthyroid rats were observed despite low glycogen concentrations (Fig. 2a). Nonetheless, a positive correlation between the glycogen concentration and the rate of lipogenesis ($P < 0.01$) existed in hyperthyroid rats, even though the glycogen concentration varied over a range (0–100 glucosyl units/g) where there was no such correlation in euthyroid rats.

Glycogenesis versus lipogenesis

Lipogenesis and glycogenesis can both be measured by the incorporation of ^3H from $^3\text{H}_2\text{O}$ into product (fatty acid or glycogen). Consequently, it is possible to determine the simultaneous rates of these processes. Although increases in both glycogen synthesis and lipogenesis are observed within the first 3 h of re-feeding in euthyroid rats, there is a greater stimulation of glycogenesis (G) than of lipogenesis (L). This is demonstrated by an increase in the value of G/L (Fig. 2b; see also Fig. 1a). Subsequently there is a steady decline in the value of G/L, indicating a re-direction of carbon flux towards lipogenesis. From Fig. 2(c), it appears that in euthyroid rats low rates of lipogenesis are observed when rates of glycogen synthesis exceed 50 μg -atoms of 'H'/h per g (equivalent to about 15 μmol of glucosyl units/h per g; Postle & Bloxham, 1980). However, although rates of lipogenesis were high at glycogenic rates of less than 50 μg -atoms of 'H'/h per g, there was still a negative correlation between glycogenesis and lipogenesis ($P < 0.001$). In the glycogen synthase-deficient (*gsd/gsd*) rat, where glycogen concentrations are high with consequent inhibition of glycogen synthase and glycogenesis, high rates of lipogenesis are observed within 1 h of glucose administration (Holness *et al.*, 1987b). This situation resembles that occurring during later times after re-feeding. It is therefore suggested that the negative correlation reflects a controlling influence of glycogenesis on lipogenesis (or vice versa).

In hyperthyroidism there was a shift in emphasis from glycogenesis to lipogenesis during the first 3 h after the provision of chow (Fig. 2b). A significant rise in G/L was no longer observed. It can therefore be concluded that there is equal stimulation of ^3H incorporation into glycogen and fatty acid. This is reflected in the plot of lipogenesis versus glycogenesis (Fig. 2c). A negative correlation between lipogenesis and glycogenesis at low rates of glycogen synthesis (< 50 μg -atoms of 'H'/h per g) was again observed ($P < 0.01$).

Conclusions

Previous studies have indicated that 6-phosphofructo-2-kinase activity is either unchanged (Hue *et al.*, 1984) or

increased (Claus *et al.*, 1984; Kuwajima *et al.*, 1986) after re-feeding. Where increases in activity have been observed, they have been correlated with increases in the insulin/glucagon concentration ratio (Claus *et al.*, 1984; Kuwajima *et al.*, 1986). However, 6-phosphofructo-2-kinase is not unique in its sensitivity to changes in the insulin/glucagon ratio; pyruvate kinase activity is also affected. Importantly, increases in pyruvate kinase have been observed concurrently with activation of 6-phosphofructo-2-kinase (Claus *et al.*, 1984), and occur within 2 h of re-feeding (Claus *et al.*, 1984; Holness & Sugden, 1987a), whereas increases in Fru-2,6- P_2 concentrations are not observed for at least 4 h. This suggests that a further mechanism may operate to restrict increases in Fru-2,6- P_2 concentrations. This may involve the preferential use of hexose phosphates for glycogen synthesis, made possible by the differential sensitivity of glycogen synthase and Fru-2,6- P_2 formation to carbohydrate provision (Hue *et al.*, 1984). It is necessary to suggest that hexose phosphate supply is limiting for Fru-2,6- P_2 formation for up to about 4 h after re-feeding. At the end of this period, effects of an increased glycogen concentration to inhibit glycogen synthase and therefore the utilization of hexose phosphate for glycogen synthesis, possibly coupled with increased glucose 6-phosphate production from glucose (Minderop *et al.*, 1987), would be expected to lead to hexose phosphate accumulation, and thereby to permit Fru-2,6- P_2 formation.

The present work demonstrated a positive correlation between glycogen concentration and lipogenesis, and a negative correlation between glycogenesis and lipogenesis. It is unknown whether the effects of glycogen on lipogenesis are direct or secondary to inhibition of glycogen synthase. The regulatory interaction between glycogenesis and lipogenesis also remains unclear.

The lower rates of glycogenesis observed after re-feeding did not elicit the expected rise in Fru-2,6- P_2 concentrations in hyperthyroid rats, suggesting that there might be reactions other than glycogen synthase and 6-phosphofructo-2-kinase competing for hexose phosphate. In view of T_3 -induced increases in the activities of glucose-6-phosphatase and glucose-6-phosphate dehydrogenase, it is suggested that the relative contribution of glycogen synthase to the control of hexose phosphate concentration is diminished, whereas that of glucose-6-phosphatase and/or glucose-6-phosphate dehydrogenase is increased.

Fig. 2(c) shows that the relationship between glycogenesis and lipogenesis is similar in euthyroid and hyperthyroid rats. The increased rate of lipogenesis observed immediately after chow re-feeding in T_3 -treated rats could therefore be predicted simply on the basis of diminished glycogenesis. Thus, at equivalent glycogenic rates (e.g. at 2 h after re-feeding in hyperthyroid rats and at 6 h after re-feeding in euthyroid rats; see Fig. 1a), rates of lipogenesis are approximately equal (see Table 1). The effect of hyperthyroidism would appear to be an acceleration of the hepatic response to re-feeding. This is emphasized from the plots of Fru-2,6- P_2 and G/L versus time (Figs. 1a, 2c) and supported by the more rapid re-activation of the hepatic pyruvate dehydrogenase complex (Holness & Sugden, 1987a).

This work was supported by a project grant from the U.K. Medical Research Council. We acknowledge the help of Dr.

P. A. MacLennan and Dr. Da-Yong Jin, and the secretarial assistance of Lena Purvis.

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Received 20 November 1987/15 January 1988; accepted 2 February 1988