We have recently cloned the murine glucagon receptor (GR) gene and shown that it is expressed mainly in liver. In this organ, the glucagon-GR system is involved in the control of glucose metabolism as it initiates a cascade of events leading to release of glucose into the blood stream, which is a main feature in several physiological and pathological conditions. To better define the metabolic regulators of GR expression in liver we analyzed GR mRNA concentration in liver in the rat and in the mouse. First, we report that the concentration of the GR mRNA progressively increased from the first day of life to the adult stage. This effect was abolished when newborn rodents were fasted. Second, under conditions where intrahepatic glucose metabolism was active such as during fasting, diabetes, and hyperglycemic clamp, the concentration of GR mRNA increased independent of the origin of the pathway that generated the glucose flux. These effects were blunted when hyperglycemia was corrected by phlorizin treatment of diabetic rats or not sustained during euglycemic clamp.

In accordance with these observations, we demonstrated that the glycolytic substrates glucose, mannose, and fructose, as well as the gluconeogenic substrates glycerol and dihydroxyacetone, increased the concentration of GR mRNA in primary cultures of hepatocytes from fed rats. Glucagon blunted the effect of glucose without being dominant. The stimulatory effect of those substrates was not mimicked by the nonmetabolizable carbohydrate L-glucose or the glucokinase inhibitor glucosamine or when hepatocytes were isolated from starved rats. In addition, inhibitors of gluconeogenesis and lipolysis could decrease the concentration of GR mRNA from hepatocytes of starved rats. Combined, these data strongly suggest that glucose flux in the glycolytic and gluconeogenic pathways at the level of triose intermediates could control expression of GR mRNA and participate in controlling its own metabolism.

In Vivo and in Vitro Regulation of Hepatic Glucagon Receptor mRNA Concentration by Glucose Metabolism

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The glucagon receptor (GR) is a 63,000-Da plasma membrane protein that belongs to a subfamily of peptide hormone receptors (1, 2). All members of this family contain seven transmembrane domains and are coupled with GTP-binding proteins. Upon binding to its receptor, glucagon initiates its action by activating several GTP-binding proteins which are rate-limiting steps in various signal transduction cascades (3–12).

The GR gene is expressed mainly in liver (2, 8, 13, 14) where it initiates a cascade of events leading to synthesis and release of glucose into the blood stream (15). Hepatic glucose production represents a major process in several physiological and pathological conditions. In newborns, glucagon is secreted within an hour of parturition and initiates several processes leading to hepatic glucose production (16) from glycogenolysis and gluconeogenesis (17). Then, during suckling glucagon stimulation ensures hepatic synthesis of glucose, which is otherwise poorly provided by mother’s milk (18). Similarly, during starvation in adults glucose produced by the liver is the main energy source utilized by splanchic tissues and brain (19). In pathological situations such as diabetes, elevated hepatic glucose production is one of the key features responsible for hyperglycemia (20). The GR is also expressed in pancreatic beta cells where its stimulation potentiates insulin secretion (21). Therefore, the GR plays a major role in regulation of glucose homeostasis. To more accurately understand its role(s) in regulation of glucose metabolism, we measured modulation of GR mRNA concentration in liver. We analyzed variations in hepatic GR mRNA concentration in mouse under physiological conditions and in rat under experimental conditions and primary cultures of hepatocytes to further define the in vivo conclusions.

MATERIALS AND METHODS

In Vivo Studies in Mice

Mice (CBA) bred in our laboratory were housed at 24 °C with light from 0700 to 1900 h and free access to water and chow (72% carbohydrate, 1% fat, 27% protein; in percent of energy). To follow GR mRNA concentration during development 16-, 17-, 18-, and 19-day-old fetuses and 1-, 10-, 15-, 20-, and 28-day-old mice were sacrificed by cervical dislocation, and the livers were removed and frozen (n = 2–6/group). To study the influence of nutritional variations on GR mRNA concentration in liver, mice (n = 18) were weaned either with a high fat diet (n = 6) (18% carbohydrate, 58% fat, 24% protein; in percent of energy) or a high carbohydrate diet (n = 6) (63% carbohydrate, 11% fat, 26% protein; in percent of energy) (22). The livers were removed and frozen. In addition, mice (n = 6) were sacrificed during the dark period of their daily light cycle to ensure a fed state, and they are referred to as controls. Mice were sacrificed following a 2-day fast (n = 6) or fasted for 2 days and reared for 1 day (n = 5) and sacrificed in the postprandial state.

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1 The abbreviations used are: GR, glucagon receptor; MPA, mercaptoprolinate; STZ, streptozotocin.

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Fig. 1. Developmental and nutritional regulation of the liver GR mRNA concentration in vivo. Northern blot analysis (left panels) of the in mouse liver. Quantification of liver GR mRNA in arbitrary units of the described mice is shown on the right panels. A and B, RNA from 16–19-day-old fetuses (f16–f19) and suckling 1-, 10-, 15-, 20-day-old and fed adult mouse liver were analyzed. 16-day-old fetuses were set as 100%. Four to six mice per group were studied. C, RNA from livers from 20-day-old mice and mice weaned onto a normal (NC), high fat (HFC), or high carbohydrate (HCC) diet were analyzed. Six mice per group were studied. NC were set as 100%. D, RNA from livers from mice fed (Control), 2 days fasted (2 D.Fast), and 1-day refed after a 2-day fast (1 D.Refed) were analyzed. Five to six mice per group were studied. Controls were set as 100%. The asterisk (*) indicates statistical significance for \( p < 0.05 \) between control and experimental group.

In Vivo Studies in Rats

One-day-old Wistar rats were fasted for 16 h \( (n = 9) \), and livers from these and 1-day suckling rats were removed and frozen.

Diabetes Induction—Diabetes was induced by an intraperitoneal injection of 65 mg/kg of body weight of streptozotocin (STZ, Sigma) dissolved in 0.1 M ice-cold sodium citrate \((23, 24)\). To avoid the lethality of hyperglycemia and hyponinsulinemia characteristic of long term insulin-dependent diabetes, female Wistar rats were mated at 9 weeks of age prior to injection of STZ. Indeed, development of insulin resistance during pregnancy may protect the mother from the deleterious effect of a lack of insulin \((25, 26)\). In addition, elevated ketones are redistributed to the fetus to be used as fuel, which may be less deleterious to the mother \((27, 28)\). The mating day was considered as day 1 of gestation and STZ injection. On day 3 post-STZ injection, blood was sampled from the tail vein, and diabetes was diagnosed when plasma glucose levels were greater than 16 mm. Diabetic rats \( (n = 9) \) were randomly chosen to receive a continuous subcutaneous infusion of phlorizin, an inhibitor of renal tubular glucose reabsorption (STZ, Sigma). Phlorizin, dissolved in a 40% \((w/v)\) propylene glycol solution, was delivered at a rate of 0.4 mg/kg/day, via implantable osmotic pumps \((Alzet, Charles River St. Aubin les Ebeuf, France)\). Upon completion, rats were sacrificed by cervical dislocation, livers immediately removed, frozen in liquid nitrogen, and stored at \(-80^\circ C\).

Insulin and Glucose Infusions—Indwelling catheters were inserted into the left jugular vein and right carotid artery under light ether anesthesia so six 1-day-pregnant female Wistar rats could recover rapidly from surgery and be studied conscious. Clampers were performed on day 19 of pregnancy for 12 h as described previously \((29)\). Blood samples were withdrawn from the carotid artery and glucose concentration checked with a glucose reflectance meter \((One Touch II, LifeScan, Inc., Johnson & Johnson, Milpitas, USA)\). Upon completion, rats were sacrificed by cervical dislocation, livers immediately removed, frozen in liquid nitrogen, and stored at \(-80^\circ C\). All rats were sacrificed in the postprandial state and referred to as controls.

Primary Culture of Rat Hepatocytes

Isolation—Hepatocytes were isolated from Wistar rats weighing 200 g at 0900 h, i.e. postabsorptive period or after a 24-h food removal, as described previously \((29)\). Cell viability, estimated by trypan blue exclusion, was greater than 90%.

Primary Culture—Hepatocytes were isolated from fed rats and suspended in Medium 199 containing Earle’s salt, 2.2 mg/liter NaHCO3 \((Life Technologies, Inc., Cergy-Pontoise, France)\) with penicillin \((100 \mu g/ml)\), streptomycin \((100 \mu g/ml)\), kanamycin \((50 \mu g/ml)\), and supplemented with 2% Ultroser \((Life Technologies, Inc., Cergy-Pontoise, France)\). Hepatocytes were plated 8 \times 10^6 cells/100-mm² dish. After cell attachment \((4 \text{ h})\), the medium was replaced with fresh Medium 199 containing hormones and nutrients as described in the figure legends. The inhibitors of gluconeogenesis mercaptopicolinate \((MPA, dissolved in 150 mM HEPES and used at 1 mM)\) and lipolysis tetradecylglycidate \((dissolved in 100% dimethyl sulfoxide and used at 40 \mu M)\) were added as indicated.

Quantification of Glucagon Receptor and GLUT2 mRNA

Total RNAs were isolated using a guanidine thiocyanate method and stored at \(-80^\circ C\) until use \((30)\). Total RNAs \((20 \mu g)\) were denatured, size-fractionated by electrophoresis, and transferred to nylon. The GLUT2 cDNA probe \((31)\) was a gift from Dr. B. Thorens. Probes were labeled with [32P]dCTP using the Multiprime labeling system \((Amersham, Bucks, UK)\). Hybridizations were performed in solutions containing 42% deionized formamide, 7.5% dextran sulfate, 8 \times 10^6 cells/100-mm² dish. After cell attachment \((4 \text{ h})\), the medium was replaced by fresh Medium 199 containing hormones and nutrients as described in the figure legends. The inhibitors of gluconeogenesis mercaptopicolinate \((MPA, dissolved in 150 mM HEPES and used at 1 mM)\) and lipolysis tetradecylglycidate \((dissolved in 100% dimethyl sulfoxide and used at 40 \mu M)\) were added as indicated.

Statistical Analysis

Results are expressed as means \( \pm S.E. \) Statistical analysis were performed by Student’s \( t \) test for unpaired data. Statistical significance was reached for \( p < 0.05 \).

RESULTS

GR mRNA Concentration in Mouse Liver during Development—Traces of GR mRNA could be detected as early as 16 days of fetal life (Fig. 1A). The concentration of a 1.9-kilobase pair GR mRNA increased from the first day of postnatal life to adulthood (Fig. 1B). Some variability in the concentration of GR mRNA is observed at birth. When the mice were either weaned onto a high fat or high carbohydrate diet the concen-
Quantification of liver GR mRNA concentration in experimental conditions. Northern blot analysis of the GR mRNA concentration in rat liver (left panels). Quantification of liver GR mRNA in arbitrary units of the described rats is shown in the right panels. A, 1-day-old newborn rats were fasted for 16 h (NB1 Fasted) and compared with 1-day-old newborn rats suckling the mother’s milk (NB1 Suckling). Eight rats per group were studied. NB1 Suckling was set as 100%. B, hyperglycemic hypoinsulinemic diabetic rats (STZ) and normoglycemic hypoinsulinemic phlorizin treated diabetic rats (STZ-Phlo) were compared with rats in postprandial state (Control). 18 S rRNA is shown to correct for loading differences between lanes. Six rats per group were studied. Controls were set as 100%. C, 12-h hyperinsulinemic hyperglycemic (HG) and 12-h hyperinsulinemic normoglycemic (HI) clamped rats were compared with rats in the postprandial state (Control). 18 S rRNA is shown to correct for loading differences between lanes. Six rats per group were studied. Controls were set as 100%. The asterisk (*) indicates statistical significance for p < 0.05 between control and experimental groups.

First, 1-day-old newborn rats were fasted for 16 h. This treatment induced a dramatic decrease in liver GR mRNA concentration when compared with suckling rats (Fig. 2A). To analyze the effect of glycemic variations on liver GR mRNA concentration, STZ was injected to female rats to achieve hyperglycemia and induce hypoinsulinenia. Nineteen days after STZ injection plasma glucose level rose from 5.0 ± 0.1 mM to 27.0 ± 1.2 mM and insulin level dropped from 224 ± 18 ppt to 42 ± 66 ppt. Diabetes increased the concentration of GR mRNA by 250% in rat liver (Fig. 2B). When hyperglycemia was reduced from 27 to 12 mM by phlorizin treatment GR mRNA concentration decreased to reach a level similar to the control nondiabetic rats (Fig. 2B).

The effect of hyperinsulinenia (4.5 nM) in the presence or absence of hyperglycemia (26 mM) was tested at the end of 12 h of hyperinsulineemic euglycemic or hyperinsulinemic hyperglycemic clamp conditions. Hyperglycemia was necessary to maintain elevated GR mRNA concentration in rat liver after 12 h of hyperinsulinenia (Fig. 2C).

In Vitro Analyses—To further dissect apart the effect of carbohydrate metabolism on the concentration of GR mRNA, primary cultures of rat hepatocytes were prepared. In hepatocytes cultured for 24 h the concentration of GR mRNA rose proportionally to increasing concentrations of glucose in the medium (Fig. 3A). Similar results were obtained when hepatocytes were cultured in the presence or absence of 10% fetal bovine serum (data not shown). Fructose and mannose induced the same stimulatory effect on GR mRNA concentration when present at 5 mM but not 25 mM (Fig. 3A). Conversely, the concentration of GLUT2 mRNA further increased under these conditions, suggesting that these two genes are differentially regulated (Fig. 3B). Incubation of hepatocytes with glucosamine, which inhibits glucokinase activity, was associated with a decrease in GR and GLUT2 mRNA concentrations. But, increasing the intracellular concentration of carbohydrate 6-phosphate by adding 2-deoxyglucose to the medium did not further increase the concentration of GR or GLUT2 mRNA (Fig. 3B). Similarly, l-glucose which is not metabolized did not influence the concentrations of GR or GLUT2 mRNA (Fig. 3B).

The presence of 25 mM glucose progressively increased the concentration of GR mRNA within 24 h (Fig. 4). Such an
Regulation of Hepatic Glucagon Receptor mRNA

increase was not observed when hepatocytes were cultured in the absence of glucose (Fig. 4). The effect of insulin was assessed after 24 h of culture in the presence of several glucose concentrations and no changes were observed (Fig. 5).

When hepatocytes were isolated from fed rats and cultured in the absence of glucose but in the presence of the gluconeogenic substrates alanine dihydroxyacetone or glycerol, the concentration of GR mRNA increased (Fig. 6A). Interestingly, this effect was not observed in hepatocytes isolated from starved rats suggesting that the basal concentration of the GR mRNA, being already elevated due to the fasting state, could not be further increased under such conditions. Conversely, the concentration of GR mRNA was decreased when a gluconeogenic inhibitor MPA was added to the hepatocytes isolated from starved rats (Fig. 6B). The same results were obtained in the presence of tetradeacylglycinate, an inhibitor of carnitine palmitoyltransferase-1, which reduces the oxidation of long chain acyl-CoA (Fig. 6B). In addition, when glucagon was added to hepatocytes isolated from fed rats it blunted the stimulatory effect of glucose without being dominant (Fig. 6C).

The stimulatory effect of glucose was further analyzed in the presence of cycloheximide to inhibit the translation process. In the presence of 20 mM glucose, when cycloheximide was added to the medium the concentration of GR mRNA further increased and a secondary signal of approximately 2.2 kilobase pairs was detected suggestive of alternative splicing of non-translated exons (Fig. 7).

DISCUSSION

We report an analysis of the regulation of GR mRNA concentration in vivo in liver and in vitro in primary cultures of hepatocytes under various metabolic conditions which more accurately define the regulation of the glucagon-GR system.

GR mRNA was detected in liver from the first day of postnatal life and its concentration reached a maximum at the adult stage (Fig. 1). The perinatal period is associated with dramatic changes in hormonal and metabolic factors (16, 17). In the newborn, after a brief period of starvation, a drop in circulating glucose and insulin levels and an abrupt secretion of glucagon occur (16). Then the newborn pup feeds on a high fat, low carbohydrate diet of mother’s milk. These hormones stimulate the synthesis and release of glucose by liver, initially from the breakdown of glycogen stores and then from neosynthesis of glucose using glycerol and amino acids as a carbon source needed by mother’s milk (17). In addition, to meet energy needs of the newborn, the capacity for fatty acid oxidation develops rapidly after birth by many tissues including liver where it results in a high rate of ketone body production (17). Liver GR mRNA increased markedly in 16 h milk fed newborns, whereas the increase was prevented when pups were fasted from birth (Fig. 3A). Interestingly, after a 16-h fasting period the concentration of GR mRNA dramatically decreased (Fig. 3A). In this condition glycogen stores were depleted and plasma free fatty acids and the rate of lipid oxidation were very low (17). The carbon substrates, in the form of low circulating concentrations of glycerol and amino acids necessary to fuel the gluconeogenesis pathway, were no longer supplied by mother’s milk (17). As a main consequence blood glucose levels remained low. This important finding suggests that impairment of the increase in GR mRNA concentration could be due to low circulating blood glucose and free fatty acid concentrations. Stimulation of glucose and free fatty acid metabolism in liver could trigger and progressively increase the concentration of GR mRNA. This switch is important as it could mediate the characteristic gluconeogenic effect of glucagon during the suckling period by initiating GR mRNA expression at birth. Conversely, in adult mice, the fasting state induced an opposite effect by increasing GR mRNA concentration in liver (Fig. 1D). Under these conditions lactate and gluconeogenic amino acid substrates are adequately available. As a consequence, gluconeogenesis is very active and GR mRNA concentration is elevated compared with mice studied in the post-prandial state despite low blood glucose concentrations (33). This suggests that flux of glucose and its metabolism in liver, rather than the glucose level per se, could regulate expression of the GR gene. Similarly, increasing liver gluconeogenesis and lipid metabolism using a high fat, low carbohydrate diet further increased the concentration of GR mRNA (Fig. 1C). The same observation was made in STZ-treated diabetic rats (Fig. 2B), a situation where gluconeogenesis and lipolysis are indeed dramatically stimulated (34). Interestingly, partial correction of hyperglycemia with the glucosuric agent phlorizin restored to normal the concentration of GR mRNA (Fig. 2B). In the condition of long term phlorizin infusion, the concentration of circulating glucagon decreased and GLUT2, glucokinase, glucose 6-phosphatase, and phosphoenolpyruvate carboxykinase mRNA levels were partially or fully normalized as a consequence of gluconeogenesis (35–37). Similarly, liver function, as measured by glucose production, was corrected (38). These in vivo results suggest that an intermediary metabolite or a factor involved in the gluconeogenic/glycolytic pathways could mediate the increase in GR mRNA concentration in liver. It has recently been demonstrated that elevated plasma free fatty acid levels could stimulate expression of genes such as carnitine palmitoyltransferase I (39).

To determine if this increase was indeed linked to the glu-
coneogenic pathway, rats were studied under conditions where gluconeogenesis was totally inhibited such as during insulin infusion (40–42). After 12 h of hyperinsulinemia hepatic glucose production was totally inhibited and the concentration of GR mRNA remained normal or slightly lower than in control post-prandial rats. Simultaneous infusion of glucose to induce hyperglycemia and stimulation of glucose metabolism in liver was necessary to maintain a high concentration of GR mRNA (Fig. 2C). Most of the data reported here show that GR mRNAs increase in vivo under gluconeogenic conditions (i.e. suckling newborns, fasting, diabetes).

The above results further emphasize that glucose, beside its role as a nutrient, could regulate, through some intermediates of its metabolism, GR gene expression (43, 44). This observation is reinforced by our in vitro results and data from others (45), which showed that glucose increased GR mRNA concentration in primary cultures of hepatocytes (Fig. 3). Glucose in liver is mainly metabolized by the rate-limiting enzyme glucokinase (46). Interestingly, mannose and fructose, which do not need glucokinase to be metabolized, increased glucose 6-phosphate concentration (Fig. 8) (47, 48) and gave similar results with lower concentration of the carbohydrate (Fig. 3A). It is noteworthy that these carbohydrates at high concentration decreased GR mRNA concentration. This could be associated with a depletion of ATP content (49) and an inhibition of glucokinase activity (47, 50–52). This effect was not observed for GLUT2 expression, stressing the differential regulation of the two genes (Fig. 3A). The increase in GR mRNA concentration could not be mimicked by the nonmetabolizable sugar L-glucose or by glucosamine which inhibits glucokinase (Figs. 3, A and B). The effect of glucose was not observed when hepatocytes were isolated from 48-h fasted rats, i.e. when glucokinase activity was very low (data not shown). The stimulatory effect of glucose could also be observed over time as the concentration of GR mRNA increased when hepatocytes were cultured for 24 h in the presence of a high glucose concentration (Fig. 4). No effect was observed in the absence of glucose or when insulin was combined with glucose (Fig. 5). These results could suggest that glucokinase activity and the accumulation of its product glucose 6-phosphate contributed to the increase in concentration of GR mRNA. However, addition of 2-deoxyglucose to the medium that mainly accumulated as 2-deoxyglucose 6-phosphate did not increase the concentration of GR mRNA in primary cultures of hepatocytes. A metabolite further down the glycolytic pathway from glucose 6-phosphate and common to the gluconeogenic pathway could be responsible (Fig. 8). Indeed, when gluconeogenic substrates dihydroxyacetone or glycerol were added to primary cultures of hepatocytes isolated...
from fed rats the concentration of GR mRNA increased (Fig. 6A). In hepatocytes isolated from fed rats, dihydroxyacetone and glycerol are minimally converted into glucose but mainly converted into lactate and pyruvate (Fig. 8) (53). The same results were obtained with alanine, which further reinforces the hypothesis that a metabolite distal to glucose 6-phosphate and the flux of carbohydrate intermediates, possibly a triose, could regulate the concentration of GR mRNA. Indeed, when gluconeogenesis was inhibited at the level of PEPCK by MPA could regulate the concentration of GR mRNA. Indeed, when gluconeogenesis was inhibited at the level of PEPCK by MPA could regulate the concentration of GR mRNA. Indeed, when gluconeogenesis was inhibited at the level of PEPCK by MPA could regulate the concentration of GR mRNA. Indeed, when gluconeogenesis was inhibited at the level of PEPCK by MPA could regulate the concentration of GR mRNA. 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