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Functional Significance of Hepatocyte Heterogeneity for Glycolysis and Gluconeogenesis

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JUNGERMANN, K. *Functional significance of hepatocyte heterogeneity for glycolysis and gluconeogenesis.* PHARMACOL BIOCHEM BEHAV **18**: Suppl. 1, 409–414, 1983.—Hepatocytes from the periportal (afferent) and perivenous (efferent) zone of the liver parenchyma differ in their enzyme distribution and subcellular structures. The key enzymes of gluconeogenesis are predominant in the periportal zone, those of glycolysis in the perivenous zone. The heterogeneous expression of the genome in hepatocytes is apparently caused by the periportal to perivenous gradient in oxygen- and hormone-concentrations as well as by a different autonomic innervation of the parenchymal zones. The model of "metabolic zonation" suggests that, in concordance with the distribution of the key enzymes, gluconeogenesis would be predominantly catalyzed by periportal hepatocytes, while glycolysis would be preferentially mediated by perivenous cells. This model is corroborated by a calculation of the flux at the glucose/glucose-6-phosphate cycle *in vivo* in the periportal and perivenous zone and by a determination of the glycolytic and gluconeogenic rate in "periportal" and "perivenous" hepatocytes induced in cell culture.

Hepatocellular heterogeneity Glycolysis Gluconeogenesis Metabolic zonation

LIVER parenchymal cells appear to be rather uniform histologically; however, histochemically they show some differences. This heterogeneity has been known for many years, first on a more descriptive [17,19], then increasingly on a more functional level [9]. The following account will summarize the present evidence of (a) the heterogeneous distribution of the key enzymes of carbohydrate metabolism, (b) the induction of this heterogeneity and (c) the inverse zonal localization of glycolysis and gluconeogenesis. The metabolic heterogeneity of the liver parenchyma has been reviewed recently [5,8].

METHOD

The distribution of enzymes was determined in native liver sections with histochemical and immunohistochemical techniques [1] and in lyophilized tissue sections by microdissection followed by microbiochemical activity measurements [3, 4, 13, 14, 20].

The factors involved in the heterogeneous expression of the genome were studied in primary cultures of adult hepatocytes [12, 16, 30].

The flux rates (v) of the glucose/glucose-6-phosphate cycle were calculated on the basis of the Michaelis-Menten equation using the measured zonal concentrations of glucose and glucose-6-phosphate, the zonal activities (V_{max}) of glucokinase and glucose-6-phosphatase and the half saturating substrate concentrations (K_M) of the enzymes found in the literature. The concentrations of glucose were obtained as a first approximation by measuring the concentrations in portal ($\hat{=}$ periportal) and hepatovenous ($\hat{=}$ perivenous) blood; those of glucose-6-phosphate were calculated from the levels determined in microdissected periportal and perivenous liver tissue [10].

Hepatocytes resembling periportal and perivenous cells were induced in primary culture (48 hr) using glucagon and insulin as the major hormone [18]. Metabolic rates were determined using ^{14}C-labeled substrates [11].

RESULTS

The predominant localization of succinate dehydrogenase, a component enzyme of the citrate cycle and the respiratory chain, in the periportal zone is one of the early examples [21] of liver cell heterogeneity (Fig. 1a). In the meantime many more key enzymes and subcellular structures were found to be heterogeneously distributed [5, 8, 9]. Under the assumption that the distribution of a key enzyme indicates the predominant localization of the corresponding metabolic function, the model of 'metabolic zonation' was proposed (Table 1) [8, 9, 11].

Heterogeneous Distribution of the Key Enzymes of Glycolysis and Gluconeogenesis

The liver can be regarded as the 'glucostat' of the organism: During the absorptive phase glucose is taken up and converted to glycogen and, via glycolysis and liponeogenesis, to triglycerides. Conversely, during the postabsorptive phase, glucose is produced from the glycogen

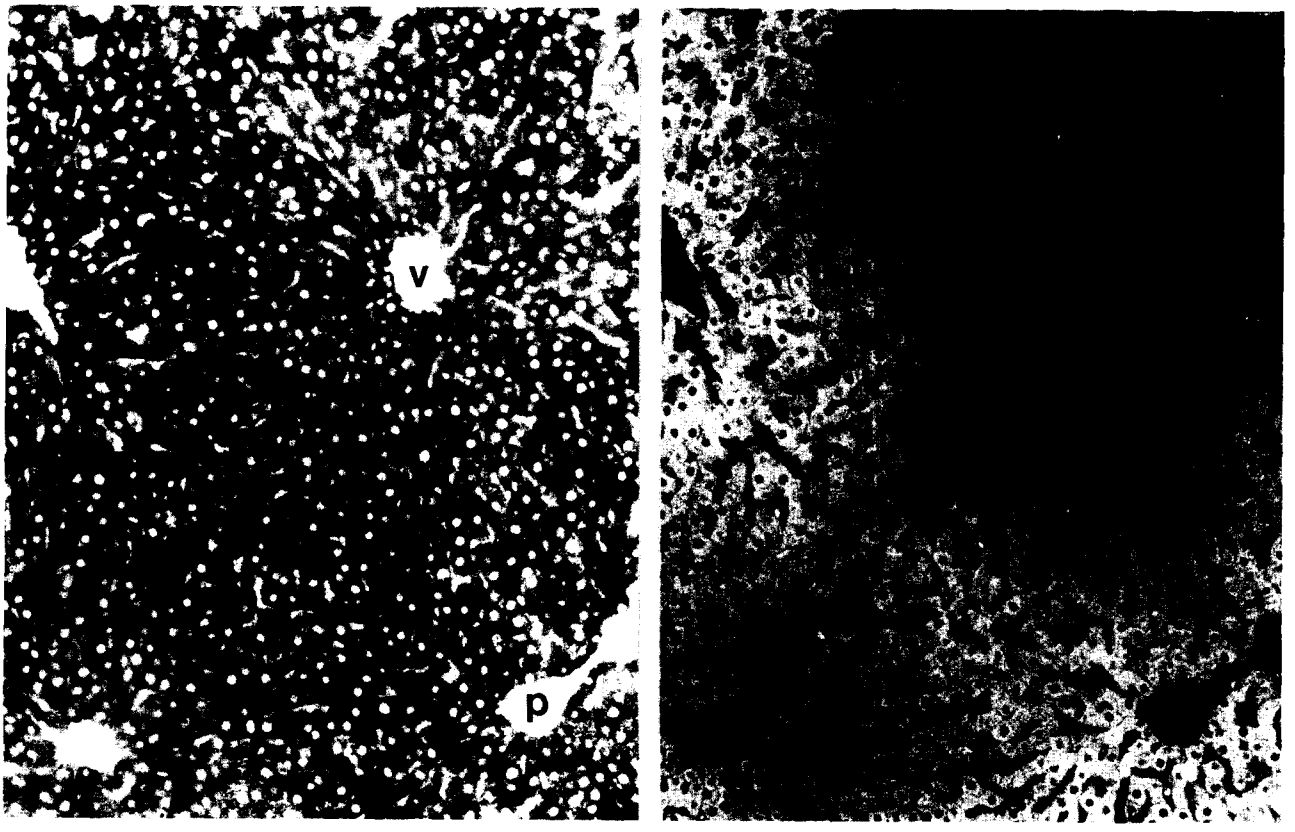

FIG. 1. Distribution of succinate dehydrogenase (SDH) and phosphoenolpyruvate carboxykinase (PEPCK) over the liver parenchyma. SDH was demonstrated histochemically with nitrobluetetrazolium chloride (a), PEPCK by indirect immunofluorescence staining (b). Liver sections (8 μm) were obtained from 24 hr starved rats. SDH (dark precipitate) and PEPCK (bright fluorescence) are both located predominantly in the periportal hepatocytes. p=Terminal portal vein; v=terminal hepatic vein. Bar 50 μm. For details see [1].

stores and, via gluconeogenesis, from lactate, amino acids and glycerol (Fig. 2).

Glycolysis. The key enzymes of glycolysis, glucokinase [3,13] and pyruvate kinase [4], are predominantly located in the perivenous zone (Fig. 2). The same holds for the key enzymes of liponeogenesis, ATP-dependent citrate lyase and acetyl-CoA carboxylase (Katz, Ick and Fischer, *Eur J Biochem,* in press and preliminary results), and for the NADPH-generating enzymes, glucose-6-phosphate dehydrogenase [26,27] and malic enzyme [27], which are functionally linked to fatty acid synthesis.

Gluconeogenesis. The key enzymes of gluconeogenesis, phosphoenolpyruvate carboxykinase [1,4], fructose-1,6-bisphosphatase [13,20] and glucose-6-phosphatase [14,25], are predominantly situated in the periportal zone (Fig. 2). Based on indirect evidence it is generally assumed that the zonal differences in enzyme activities, measured in microdissected tissue, are due to differences in enzyme protein content. Direct evidence using immunohistochemical techniques is provided for phosphoenolpyruvate carboxykinase (Fig. 1b) [1]. Lactate dehydrogenase [22,29] and alanine aminotransferase [22,28], which mediate the connection of lactate and alanine to the gluconeogenic pathway proper, also show higher activities in the periportal zone.

Induction of Liver Cell Heterogeneity

All hepatocytes have, of course, the same genome. Its heterogeneous expression is most likely caused by various factors such as oxygen gradient and hormone gradients and autonomic innervation.

Oxygen gradient. The liver is supplied by a mixture of arterial (pO_2=95 mm Hg) and portovenous (pO_2~50 mm Hg) blood (normally 25%:75%), which leaves the organ via the hepatic vein (pO_2~30 mm Hg) [16]. The influence of physiological oxygen tensions on the hepatocyte genome was studied in cell culture. The "periportal" enzymes phosphoenolpyruvate carobxykinase and tyrosine aminotransferase were induced by glucagon to higher levels under arterial than under venous oxygen tensions [16]. These findings indicate that different physiological oxygen tensions can modulate the induction of liver enzymes and can thus contribute to liver cell heterogeneity.

Hormone gradients. Hormones such as insulin, glucagon, catecholamines or corticosteroids are degraded during liver passage, so a hormone concentration gradient decreasing from the periportal to the perivenous area is expected. This gradient offers a ready explanation for the preferential induction of enzymes in the periportal zone, e.g. phosphoenolpyruvate carboxykinase, fructose-bisphosphatase or glucose-6-phosphatase; however, a simple explanation for the predominance of enzymes in the perivenous zone, e.g. glucokinase and pyruvate kinase, is not apparent (Fig. 2). It has been suggested that the higher level of an enzyme in the perivenous zone could be effected by an increase of the ratio

TABLE 1
METABOLIC ZONATION OF LIVER PARENCHYMA

Periportal zone	Perivenous zone
Glucose release	Glucose uptake
Glycogen degradation to glucose	Glycogen synthesis from glucose
Gluconeogenesis	Glycolysis
	Liponeogenesis
Oxidative energy metabolism	
Fatty acid oxidation	
Citrate cycle	
Respiratory chain	
Amino acid utilization	Ammonia detoxification
Aminoacid conversion to glucose	
Amino acid degradation	
Ureagenesis from amino acid nitrogen	Ureagenesis from ammonia nitrogen
Oxidation protection	Biotransformation
Cholic acid excretion	
Bilirubin excretion	

Predominant localization of major functions.

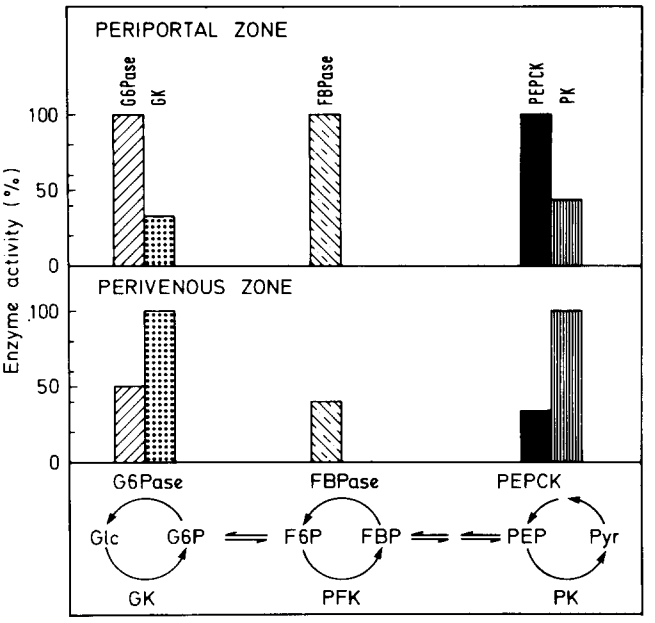

FIG. 2. Distributions of the key enzymes of glycolysis and gluconeogenesis over the liver parenchyma of fed rats. Enzyme activities were determined in microdissected liver tissue with microbiochemical techniques. In order to facilitate comparison the originally measured activities were all extrapolated to 37° assuming a doubling of activity per 10°C temperature increase and converted from dry to wet weight using a factor of 0.3; the following values (μmol · min^{-1} · g^{-1} wet weight, 37°) were obtained: glucokinase (GK) + hexokinase (HK) 1.7 periportal (pp), 3.4 perivenous (pv) [10,13], glucokinase 1.0 pp, 3.0 pv [3], glucose-6-phosphatase (G6Pase) 10.7 pp, 4.7 pv [10,14], fructosebisphosphatase (FBPase) 11.7 pp, 6.1 pv [13] and 10.5 pp, 3.0 pv [20], pyruvate kinase (PK) 84 pp, 193 pv, phosphoenolpyruvate carboxykinase (PEPCK) 7.7 pp, 2.7 pv [4]. In each case the higher value is set to 100%. Glc=glucose, G6P=glucose-6-phosphate, F6P=fructose-6-phosphate, FBP=fructose-1,6-bisphosphate, PEP=phosphoenolpyruvate, Pyr=pyruvate.

of antagonistic hormones such as insulin and glucagon [12]. This suggestion was based on the finding that the induction of glucokinase by insulin is strongly inhibited by glucagon [12] and that there appear to be conditions under which the degradation of insulin by the liver is smaller than that of glucagon (Balks, J. and K. Jungermann, preliminary data) [24]. Besides the gradients of hormone concentrations in the blood, gradients of hormone receptor densities on the liver cells might also be involved in the induction of hepatocellular heterogeneity. Yet, so far nothing is known about the zonal distribution of hormone receptors.

Autonomic innervation. Hepatocytes are innervated both by the sympathetic and parasympathetic nervous system [15]. Strong evidence is available for direct neural short-term regulation of hepatic glycogen metabolism [2, 7, 15]. It is therefore feasible that the nerves also exert trophic long-term effects [6] on the liver parenchyma. Electrical stimulation of the ventromedial hypothalamus and subsequently of the sympathetic system led after 4 hr to an increase of phosphoenolpyruvate carboxykinase (PEPCK) and to a decrease of pyruvate kinase (PK) activity, while stimulation of the lateral hypothalamus leading to activations of the parasympathetic system resulted in a decrease of PEPCK without a change of PK activity [23]. Furthermore, norepinephrine in concentrations as high as can be expected to occur in a synapse, was found to induce PEPCK in hepatocyte cultures [30]. Although the findings on enzyme induction after hypothalamic stimulation and in cell culture may be quite suggestive, convincing evidence for a direct neural long-term control of gene expression in liver is still missing.

Inverse Zonal Localization of Glycolysis and Gluconeogenesis

The functional significance of liver cell heterogeneity was first proposed for carbohydrate metabolism in the model of metabolic zonation [11] and was later extended to other functions (Table 1). The model could be corroborated by a calculation of metabolic flux at the glucose/glucose-6-phosphate cycle in the periportal and perivenous zone and by a determination of the flux of gluconeogenesis and glycolysis in hepatocytes induced in cell culture to an enzyme pattern resembling that of periportal or perivenous cells.

Flux differences at the glucose/glucose-6-phosphate cycle in periportal and perivenous zones. Flux rates were calculated on the basis of the Michaelis-Menten equation (see Method Section). The calculations revealed [12] that the periportal zone during the absorptive as well as postabsorptive phase of the 24 hr feeding rhythm should always release glucose (via glycogenolysis and gluconeogenesis) and that, inversely, the perivenous zone in the two situations should always take up glucose (for glycogen synthesis and glycolysis) (Fig. 3). In the periportal zone net flux would be more sensitive to changes in glucose-6-phosphate (larger distances of curves in Fig. 3; left panel as compared to right panel); in the perivenous zone net flux would be more sensitive to changes in glucose concentrations (steeper curves in Fig. 3; right panel as compared to left panel). During the shift from the absorptive to the postabsorptive phase the periportal glucose output would be increased and the perivenous

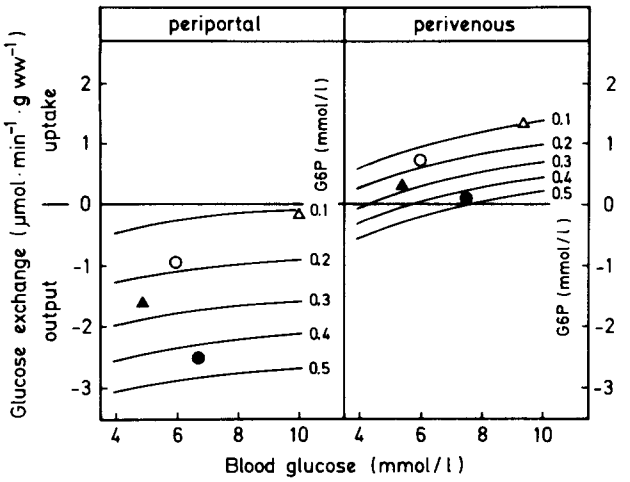

FIG. 3. Dependence of the net flux of glucose in the periportal and perivenous zone of rat liver parenchyma on the concentrations of blood glucose and of cytosolic glucose-6-phosphate. Net flux is given by the difference between the flux of the glucokinase and of the glucose-6-phosphatase reaction, as calculated by the Michaelis-Menten equation (see Method section). The range of substrate concentrations considered for glucose was 4–10 mM and for cytosolic glucose-6-phosphate 0.1–0.5 mM. Specific physiological conditions during a 24 hr day-night rhythm (19 hr–7 hr night and access to food): ○ fed, 9 hr, no net change in liver glycogen; ● fed, glucagon-treated, 9 hr, active glycogenolysis; △ eating, 2 hr, glycogen, synthesis; ▲ fasting, 16 hr, glycogenolysis. For details see [10].

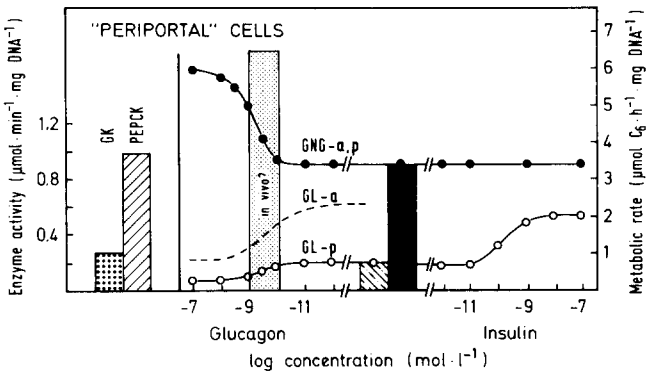

FIG. 4. Short-term effect of insulin and glucagon on glycolysis (GL) and gluconeogenesis (GNG) in cultured hepatocytes resembling periportal cells. Cells were cultured under standard conditions. Four hr and 24 hr after plating the medium was changed: "periportal" cells were induced from 24 hr–48 hr in the presence of glucagon (10^{-7}) and insulin (5×10^{-10} M). Metabolic rates were determined under postabsorptive (p) substrate conditions using 5 mM glucose and 2 mM lactate and hormones as indicated. The glycolytic rate was extrapolated to absorptive (a) conditons, e.g. 10 mM glucose and 2 mM lactate (see text). Enzyme activities (GK=glucokinase, PEPCK=phosphoenolpyruvate carboxykinase) were assayed both before and after the incubation for the study of metabolic rates; no difference was observed. Values are means of 3 cultures from a representative experiment. For details see [18].

glucose uptake would be decreased. Averaged over the total parenchyma, the expected shift from net glucose uptake to net glucose release would result.

Flux differences in "periportal" and "perivenous" hepatocytes induced in cell culture. Since isolated hepatocytes could be separated only insufficiently into periportal and perivenous cells, the attempt was made to induce in cultured hepatocytes an enzyme pattern typical of periportal and perivenous cells [18]. Glycolysis and gluconeogenesis were measured in these induced "periportal" and "perivenous" liver cells offered glucose (5 mM) and lactate (2 mM) in postabsorptive concentrations. In the absence of hormones the gluconeogenic rate was 1.6-fold higher in the "periportal" cells, while the glycolytic rate was 2-fold higher in the "perivenous" cells (Fig. 4 in comparison to Fig. 5). This finding clearly demonstrates that the different enzyme activities of the two cell types under identical substrate and product concentrations leads to quite different metabolic rates. These rates were subject to hormonal control. In both "periportal" (Fig. 4) and "perivenous" (Fig. 5) cells, insulin increased the glycolytic rate 3-fold, while it had no effect on gluconeogenesis. Glucagon decreased glycolysis to about 25% in both cell types; yet, it enhanced the gluconeogenic rate by approximately 70% only in the "periportal" cells; the "perivenous" cells were non-responsive.

In a first approximation these results may be extrapolated to the *in vivo* situation. Since "periportal" cells were obtained with glucagon and "perivenous" cells with insulin as the major hormone, it can be assumed that the short-term regulation of glycolysis and gluconeogenesis should be governed predominantly by glucagon in "periportal" and by insulin in "perivenous" hepatocytes. It should furthermore be considered that the glycolytic rate is enhanced 2–3 fold by an increase of the glucose concentration from postabsorptive (5 mM) to absorptive (10 mM) levels, while the gluconeogenic rate is not affected [18]. Thus in the "periportal" cells (Fig. 4) under the major influence of glucagon rates of gluconeogenesis of about 4.2 μmol·hr^{-1}·mg DNA^{-1} would clearly exceed rates of glycolysis of about 0.6 μmol·hr^{-1}·mg DNA^{-1} in the postabsorptive and 1.6 μmol·hr^{-1}·mg DNA^{-1} in the absorptive state. Inversely, in the "perivenous" cells (Fig. 5) under the major influence of insulin, rates of glycolysis of about 3.6 μmol·hr^{-1}·mg DNA^{-1} in the postabsorptive and 8.4 μmol·hr^{-1}·mg DNA^{-1} in the absorptive state would exceed rates of gluconeogenesis of 2.2 μmol·hr^{-1}·mg DNA^{-1}. In the postabsorptive situation, a net glucose release of 4.2 − 0.6 = 3.6 μmol·hr^{-1}·mg DNA^{-1} in the "periportal" cells would be counterbalanced by a net glucose uptake of 3.6 − 2.2 = 1.4 μmol·hr^{-1}·mg DNA^{-1} in the "perivenous" cells. In the absorptive situation, a net glucose uptake of 8.4 − 2.2 = 6.2 μmol·hr^{-1}·mg DNA^{-1} in the "perivenous" cells would be counterbalanced by a net glucose release of 4.2 − 1.6 = 2.6 μmol·hr^{-1}·DNA^{-1} in the "periportal" cells. The extrapolated values are in good agreement with the net rates of the glucose/glucose-6-phosphate cycle in the periportal and perivenous zone (Fig. 2).

DISCUSSION

It was found that the gluconeogenic key enzymes are predominant in the periportal zone and that the glycolytic enzymes are prevalent in the perivenous area (Fig. 2). It was furthermore shown that "periportal" hepatocytes induced in cell culture catalyze preferentially gluconeogenesis, while "perivenous" cells mediate predominantly glycolysis (Figs. 4 and 5). Finally, it was found that *in vivo* under normal

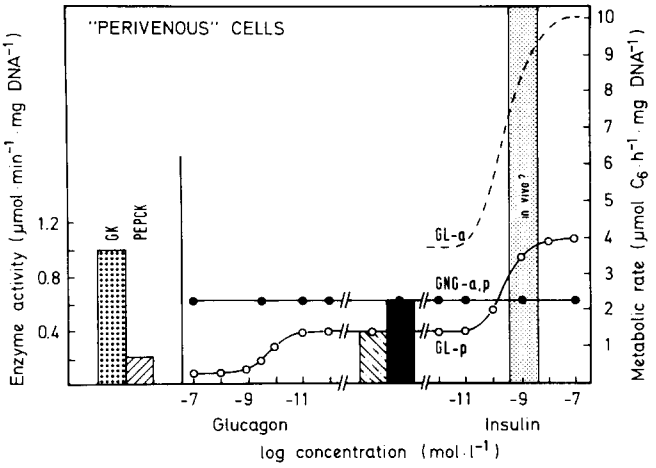

FIG. 5. Short-term effect of insulin and glucagon on glycolysis (GL) and gluconeogenesis (GNG) in cultured hepatocytes resembling perivenous cells. Cells were cultured under standard conditions. Four hr after plating the medium was changed: "perivenous" cells were induced for the following 44 hr with another medium change after 20 hr in the presence of insulin (10^{-8} M) and dexamethasone (10^{-7} M). Metabolic rates (p=postabsorptive, a=absorptive substrate concentrations) and enzyme activities (GK=glucokinase, PEPCK=phosphoenolpyruvate carboxykinase) were determined as outlined in Fig. 4. Values are means of 3 cultures from a representative experiment. For details see [18].

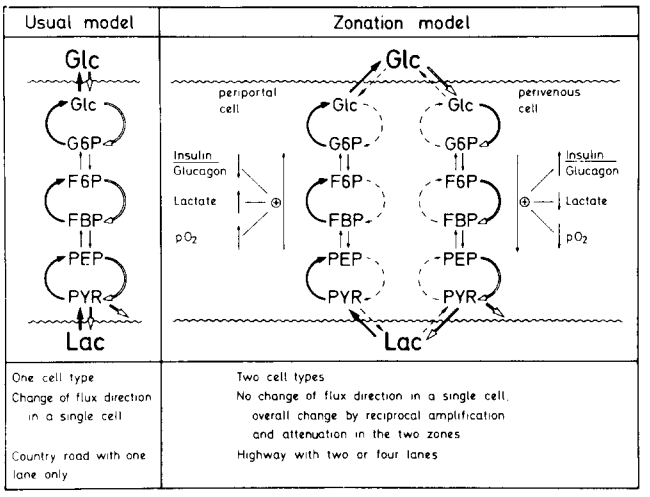

FIG. 6. Comparison of the usual and the zonation model for the reversible shift from glycolysis to gluconeogenesis. Abbreviations, see Fig. 2.

conditions the periportal cells would always be glucose-forming and that the perivenous cells would be glucose-utilizing (Fig. 3). These results corroborate the model of metabolic zonation.

In the usual model (Fig. 6), based on one type of hepatocyte possessing the same enzyme activities, the shift from net glucose uptake and glycolysis during the absorptive phase to net glucose-release and gluconeogenesis would require a change of the flux direction in the single cells. The liver would function like a narrow country road with a single lane, which allows traffic at a given time to proceed in one direction only.

In the zonation model (Fig. 6), based on the glucogenic periportal and the glycolytic perivenous hepatocytes, the reversible shift between gluconeogenesis and glycolysis would not require a change of direction of flux in the single cells. On the contrary, the shift would be brought about by amplification of one process in one zone and by simultaneous attenuation of the antagonistic process in the other zone. In this reciprocal regulation various regulatory mechanisms must be involved. Hormones, such as insulin and glucagon, would change the activities of interconvertible enzymes; effectors would influence the activities of allosteric enzymes. Since hormone and effector concentrations vary during liver passage a different regulation can be envisaged for the two zones. Thus, in the zonation model, the liver would function like a two- or even four-lane highway, which allows traffic to proceed at any given time with different rates in both directions. Maybe a highway is more efficient than a country road.

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