

HCC terminology needs to be standardized first. For example, what is an "incidental HCC"? Is this the same as a "small" HCC or an "asymptomatic HCC"? What tumor diameter should be used to define small HCC? Both 3 cm and 5 cm have been proposed. It was emphasized that not all HCCs are the same in biological behavior. They may vary depending on histological type (the fibrolamellar type is slower growing with a better prognosis), on cause (hepatitis B reactivation may occur in association with chemotherapy), on whether cirrhosis is present and perhaps on whether serum AFP values are elevated. In any trial these factors should be assessed, and perhaps patients enter into studies stratified according to some of these variables. Better means of assessing the response to therapy need to be used. One very promising approach is the use of a computer program, developed at Johns Hopkins Hospital, to measure tumor volume (10).

In summary, therapies that may significantly benefit patients with HCC are being developed. Their worth will eventually need to be tested in controlled clinical trials requiring large numbers of patients. In the developed Western world, where HCC is relatively uncommon, such trials may need to be conducted in multiple centers using standardized terminology and methodology.

ADRIAN M. DI BISCEGLIE, M.D.

Liver Diseases Section

*National Institute of Diabetes and Digestive
and Kidney Diseases*

Bethesda, Maryland 20892

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MORE ON GLUCOSE TRANSPORTERS: THE ACINAR ORGANIZATION FOR HEPATIC GLUCOSE TRANSPORT

Tal M, Schneider DL, Thorens B, Lodish HF. Restricted expression of the erythroid/brain glucose transporter isoform to perivenous hepatocytes in rats: modulation by glucose. *J Clin Invest* 1990;86:986-992.

ABSTRACT

The "erythroid/brain" glucose transporter (GT) isoform is expressed only in a subset of hepatocytes, those forming the first row around the terminal hepatic venules, while the "liver" GT is expressed in all hepatocytes. After 3 d of starvation, a three- to fourfold elevation of expression of the erythroid/brain GT mRNA and protein is detected in the liver as a whole; this correlates with the expression of this GT in more hepatocytes, those forming the first three to four rows around the hepatic venules. Starvation-dependent expression of the erythroid/brain GT on the plasma membrane of these additional hepatocytes is lost within 3 h of glucose refeeding; however, by immunoblotting we show that the protein is still present. Its loss from the surface is possibly explained by internalization.

COMMENTS

Transport of glucose across the plasma membrane of mammalian cells can occur by a secondary active transport process such as in the small intestine or by facilitated diffusion. Facilitated diffusion of glucose is mediated by a family of related transport proteins having different tissue distribution and diverse regulation. To date, five functional facilitated diffusion transport systems and a pseudogene have been identified (Table 1). These proteins vary in size from 492 amino acids to 524 amino acids (1). Among the five functional forms a 39% to 65% identity and a 50% to 76% similarity exists. Twenty-six percent of the residues are identical in all five forms, whereas 13% are conservative substitutions (1). Two species of facilitated diffusion glucose transporters have been found in the liver, a less abundant erythroid/brain form or glut-1 and the main liver form or glut-2. These forms differ considerably in the Michaelis constant (K_m) for glucose. Glut-1 has a K_m of 1 to 2 mmol/L and thus is saturated at physiological concentrations of serum glucose (about 5 mmol/L). In contrast, glut-2 has a K_m of 15 to 20 mmol/L. Therefore hepatic glucose homeostasis is subserved by the low-affinity liver isotype or glut-2.

The two rat liver isoforms respond differently to conditions of fasting and refeeding and to experimental diabetes and insulin replacement. These different patterns of response led investigators to propose that these transporters are regulated by different mechanisms (2). In this paper, the authors, using polyclonal antibodies that specifically recognize either glut-1 or glut-2, immunolocalized the hepatocytes expressing these transporters. They observed that under control conditions, glut-2 was expressed in all hepatocytes. In contrast,

TABLE 1. Mammalian glucose transporters

Glucose transporter	Major sites of expression	K_m (mmol/L)	Proposed function
Active transport			
Sgt-1 (Na ⁺ -glucose cotransporter)	Small intestine, renal tubules	0.1-10	Active uptake of glucose
Facilitated diffusion			
Glut-1	Ubiquitous, but especially RBC, brain, HepG2 hepatoma cell line	1-2	Glucose uptake into cells
Glut-2	Liver, kidney, small intestine, and β cells of pancreas	15-20	Glucose homeostasis; likely mediates bidirectional transfer of glucose by hepatocytes
Glut-3	Many tissues, including brain	< 1	Unknown
Glut-4	Muscle and fat	~5	Insulin-responsive glucose uptake
Glut-5	Small intestine and kidney placenta, and kidney	1-2	Unknown
Glut-6	mRNA nontranslatable into a functional protein		Pseudogene

glut-1 was expressed only in one or two rows of hepatocytes surrounding the hepatic venule. Fasting for 3 days resulted in an increment in the levels of glut-1 apoprotein and messenger RNA (mRNA), whereas no major changes were observed in the levels of glut-2. Furthermore, the area of hepatocytes expressing glut-1 expanded to about three to five rows of cells surrounding the hepatic venule. Glucose administration and refeeding of the fasted rats resulted in a decrease in the number of hepatocytes expressing glut-1 to a control pattern. However, the concomitant administration of glucose and food in this study does not allow one to define the role of glucose in regulating the expression of glut-1 in acinar hepatocytes.

Various aspects of this paper are of considerable interest. The restricted expression of glut-1 to a few hepatocytes surrounding the hepatic venule provides an explanation for previous observations by various groups (3, 4) of low levels of expression of this transporter in the liver. In rat liver, mRNA levels of glut-1 represent about 1% to 3% of the mRNA levels of the glut-2 transporter (2). The restricted expression of glut-1 also reinforces the proposal that the one to two rows of hepatocytes surrounding the hepatic venule represent a different state of differentiation of liver cells. It should be remembered that glutamine synthetase is also exclusively expressed in these hepatocytes (5). Therefore these genes may represent suitable models for the study of the regulation of hepatocyte-specific gene expression. Finally, the presence in all hepatocytes of glut-2 with a K_m for glucose of 15 to 20 mmol/L points to a major role for this transporter in the bidirectional transport and regulation of glucose within the hepatic acinus. Furthermore, the location in the last two hepatocytes of a glucose transporter, glut-1, with a low K_m for glucose, and thus functioning under conditions of saturation, suggests that the role of this transporter may not be the regulation of the levels of glucose reaching the systemic circulation. In contrast to glutamine synthetase, this transporter may not act in a scavenger role. Rather, the

presence of this transporter at that location may indicate the need for glucose of those cells, suggesting that "the last hepatocyte" may survive in a very different metabolic state than more proximal hepatocytes.

BAHRI BILIR, M.D.

JORGE J. GUMUCIO, M.D.

Department of Medicine

*Veterans Administration Medical Center and
the University of Michigan
Ann Arbor, Michigan 48105*

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POTENTIAL IMPORTANCE OF THE SEXUAL TRANSMISSION OF NON-A, NON-B HEPATITIS

Alter MJ, Coleman PJ, Alexander WJ, Kramer E, Miller JK, Mandel E, Hadler SC, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *JAMA* 1989;262:1201-1205.

ABSTRACT

To identify previously unrecognized sources for acquiring acute hepatitis B and non-A, non-B (NANB) hepatitis, we interviewed patients with these types of