Dysregulated hepatic expression of glucose transporters in chronic disease: contribution of semicarbazide-sensitive amine oxidase to hepatic glucose uptake

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The liver contributes to metabolic carbohydrate homeostasis, is sensitive to insulin, and is a major site for synthesis, storage, and redistribution of carbohydrates (41). Situations in which the balance of glucose homeostasis is upset, such as diabetes, can lead to metabolic disturbances that drive chronic organ damage and failure. Notably, acute liver failure is associated with profound hypoglycemia, and chronic, cirrhotic liver diseases are often associated with insulin resistance, deficient insulin clearance, and hyperinsulinemia (2, 32). This has led to investigation of the expression and function of receptors that regulate glucose uptake and release by hepatocytes, the most important cells in glucose regulation and glycogen storage under normal conditions. Expression of glucose transporters (GLUT)-1 and -2 (50, 59), GLUT9 (27), and GLUT10 (45) has been reported on hepatocytes, but little is known about their expression or function on other cell types or if their hepatic expression is modulated during disease pathogenesis.

Defining regulatory mechanisms that modify local expression of glucose transporters in tissue is important, as it can shed light on disease pathogenesis. While abnormal GLUT1 expression on tumor endothelium in hepatocellular carcinoma has prognostic and diagnostic significance (61) and diabetes in hepatitis C virus has been linked to virally induced downregulation of GLUT1 and -2 on hepatocytes (26), mechanisms leading to these alterations remain to be fully defined. One factor in particular, vascular adhesion protein-1 [VAP-1, also known as semicarbazide-sensitive amine oxidase (SSAO)] (35), may be of particular significance for hepatic glucose homeostasis. It is a multifunctional protein expressed on a variety of cells, with a secreted soluble form (sVAP-1) in serum (55). sVAP-1 is cleaved from membrane-bound VAP-1 in response to signals including TNF-α and insulin (1) and is abundant in inflammatory liver disease (34), obesity (46), and diabetes (52). VAP-1 catalyzes the oxidative deamination of endogenous [methylamine (MA) and aminoacetone (4)] and exogenous (benzylamine) primary amines (39), and, importantly, bioactive metabolites generated as a result of its amine oxidase activity can elicit insulinomimetic responses (62). Levels of sVAP-1 are increased in nonalcoholic steatohepatitis (NASH) (8), and SSAO activity is known to stimulate glucose uptake in adipocytes and smooth muscle cells as a result of translocation of GLUT4 (12) and GLUT1 to the cell membrane (10).

In the current study we have used human tissue and primary liver cells to investigate the expression of GLUTs in disease. We have also measured the expression of VAP-1 in hepatic tissue and used precision-cut liver slices (PCLS) to determine whether activation of VAP-1 in human tissue modifies hepatic glucose receptor expression and glucose uptake. We demonstrate, for the first time, alterations in hepatocellular expression of glucose and fructose transporters in CLD and provide evidence that the semicarbazide-sensitive amine oxidase (SSAO) activity of VAP-1 modifies hepatic glucose homeostasis and may contribute to patterns of GLUT expression in chronic disease.

THE LIVER CONTRIBUTES to metabolic carbohydrate homeostasis, is sensitive to insulin, and is a major site for synthesis, storage, and redistribution of carbohydrates (41). Situations in which the balance of glucose homeostasis is upset, such as diabetes, can lead to metabolic disturbances that drive chronic organ damage and failure. Notably, acute liver failure is associated with profound hypoglycemia, and chronic, cirrhotic liver diseases are often associated with insulin resistance, deficient insulin clearance, and hyperinsulinemia (2, 32). This has led to investigation of the expression and function of receptors that regulate glucose uptake and release by hepatocytes, the most important cells in glucose regulation and glycogen storage under normal conditions. Expression of glucose transporters (GLUT)-1 and -2 (50, 59), GLUT9 (27), and GLUT10 (45) has been reported on hepatocytes, but little is known about their expression or function on other cell types or if their hepatic expression is modulated during disease pathogenesis.

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MATERIALS AND METHODS

Tissue and blood samples. Tissue was obtained from patients at Queen Elizabeth Hospital. Normal tissue was surplus to transplantation or from tumor margin samples. Diseased tissue was also obtained during transplantation for end-stage disease [primary biliary cirrhosis, NASH, steatosis (fatty liver without inflammation), and alcoholic liver disease (ALD)]. For functional glucose uptake experiments with tissue slices, we used tissue from five normal donors per experiment. For expression data, tissue from three to five donors of each type (diseased or normal) was used. All samples were collected with local research ethics committee approval and informed, written patient consent. Murine tissue was obtained from C57BL/6 wild-type (WT) or VAP-1 null (VAP-1−/−) mice.

Cell culture. Peripheral blood lymphocytes were prepared according to established methodology (47). Similarly, hepatocytes (3), hepatic sinusoidal endothelial cells (HSEC) (37), biliary epithelial cells (BEC) (23), and hepatic myofibroblasts (22) were cultured from freshly harvested, collagenase-digested human liver tissue.

Adenoviral infection of human HSEC with VAP-1 constructs. Adenoviral constructs encoding WT VAP-1 and enzymatically inactive VAP-1 (Tyr471Phe) are described elsewhere (30). HSEC were cultured to confluence and infected with the constructs at optimal

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**Fig. 1.** A: immunohistochemical localization of vascular adhesion protein 1 (VAP-1) in normal liver (i), steatosis (ii), nonalcoholic steatohepatitis (NASH, iii), alcoholic liver disease (ALD, iv), and primary biliary cirrhosis (PBC, v), as well as NASH with isotype-matched control stain (vi). Fields were captured at ×10 original magnification (inset at ×40) and are representative of 3–5 cases for each disease. Arrows in iv indicate strong sinusoidal staining. B: VAP-1 mRNA expression in normal liver, steatosis, NASH, ALD, and PBC. Data represent fold change in gene expression relative to normal liver. Values are means ± SE; n = 3–5 in each group. ***P < 0.001 (by ANOVA). C: quantification of semicarbazide-sensitive amine oxidase (SSAO) activity in lysates from normal and diseased tissue. Data represent specific fluorescence reading at 30 min. Values are means ± SE; n = 3 in each group. *P < 0.05, ***P < 0.001 vs. normal (by ANOVA).
multiplicity of infection of 600 for 4 h in endothelial basal medium 2 (EBM-2, Clonetix, Lonza) supplemented with 10% FCS. For confirmation of human VAP-1 (hVAP-1) positivity after infection, trypsinized cells were labeled with mouse anti-human VAP-1 antibody (TK8-14, FITC-conjugated) or matched isotype control (IgG1-FITC).

**Amine oxidase assay.** Amine oxidase activity was measured using an Amplex UltraRed-based assay (Molecular Probes, Invitrogen). Tissue was digested in 0.2% Triton X-100 containing protease inhibitor cocktail (Sigma-Aldrich) and protein concentration was determined using a Bio-Rad DC Protein Assay according to the manufacturer’s instructions. Samples were diluted to 8 mg/ml and added to a 96-well flat-bottom plate containing a reaction mixture composed of benzylamine (2 mM), Amplex red reagent (200 μM; Amplex UltraRed, Invitrogen), and horseradish peroxidase (2 U/ml; Invitrogen) in the presence or absence of the specific VAP-1 inhibitor 2-bromoethylamine hydrobromide (BEA, 400 μM). The fluorometric reaction was measured continuously in a fluorescence microplate reader (Biotek SynergyHT) for ~3 h using 530-nm excitation and emission detection at 590 nm.

**Generation of PCLS.** Human PCLS were generated as previously described (24) using a Krumdieck tissue slicer (Alabama Research and Development). Slices were immediately transferred into Williams E medium (Sigma) supplemented with 2% FCS (Invitrogen) (19). For histological analysis, PCLS were fixed in formaldehyde prior to rapid freezing and cryosectioning into 15-μm sections.

**Glucose uptake assays.** Radiolabeled glucose uptake by PCLS or cells was assayed as described elsewhere (24). Stimulants included insulin (0.10 IU), MA (200 ng), and H2O2 (10 μM), alone or in combination with BEA (400 μM). Samples were run on a 5-min program to give tritium disintegrations per minute. Results were normalized to 500 mg of tissue. On occasion, 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (10 μM; Invitrogen) was used in place of radiolabeled glucose, and samples were analyzed on a fluorescence microplate reader (Biotek Synergy HT) using 485-nm excitation and emission detection at 528 nm. Here specific glucose uptake in response to treatment is expressed per 500 mg of tissue relative to uptake by unstimulated slices.

**Histological staining of sections.** Standard immunohistochemical staining techniques with 3,3’-diaminobenzidine substrate (24) were used to stain 15-μm cryosections cut from PCLS or 5-μm cryosections from explanted human liver tissue. Antibodies were mouse anti-human VAP-1 (5 μg/ml; Biotie), GLUT4 and -10 (10 and 2.5 μg/ml; Abcam), rabbit anti-human GLUT2 and -9 (5 and 10 μg/ml; Abcam), and secondary antibody (ImmPress Mouse/Rabbit Kit, Vector Labs). Isotype- and species-matched antibodies were used as controls, and representative images were captured using Zeiss Axiosvision software.

**PCR.** Tissue and cell samples were stored in RNAlater (Sigma) at 4°C until RNA extraction using an RNeasy MiniKit (Qiagen) according to the manufacturer’s instructions. RNA purity and integrity were quantified with a NanoDrop spectrophotometer (Thermo Fisher Scientific). mRNA expression was quantified using specific quantitative PCR (qPCR) arrays, such as the Fluidigm 96.96 Dynamic Array integrated fluidic circuit, where 125 ng of total RNA was transcribed to cDNA using the SuperScript III First-Strand Synthesis Supermix Kit (Invitrogen) according to the manufacturer’s instructions. Alternatively, samples used for the human NF-kB signaling pathway PCR kit (PAHS-025A, Qiagen) were transcribed using the RT² First-Strand Kit (SABiosciences, Qiagen), and PCR was performed according to the manufacturer’s instructions.

**RESULTS**

Human hepatic VAP-1 expression increases with disease (Fig. 1A). Expression was restricted to portal vascular regions and perisinusoidal cells in normal and steatotic samples (Fig. 1A, i and ii). NASH was associated with an increase in expression in fibrotic areas and within the sinusoids, and sinusoidal staining was particularly marked in patients with ALD (arrows in Fig. 1A, iv). Fibrotic areas in cholestatic disease, such as primary biliary cirrhosis, also showed abundant VAP-1 immunoreactivity (Fig. 1A, v). mRNA quantification (Fig. 1B) confirmed upregulation in chronic inflammatory

Fig. 2. mRNA expression for glucose transporters (GLUT)-1–13 in steatosis, NASH, and ALD. Data represent fold change in gene expression normalized to pooled endogenous controls relative to normal liver [defined as 1 (dashed line)]. Values are means ± SE; n = 5 (normal), 4 (steatosis), 3 (NASH), and 4 (ALD). *P < 0.05, **P < 0.01, ***P < 0.001 vs. normal liver (by ANOVA).
disease, but not simple steatosis, which was supported by quantification of SSAO activity in tissue lysates (Fig. 1C).

In normal liver, qPCR using Livak analysis showed expression of all GLUTs, except GLUT7 (44), with GLUT2, -8, -9, and -10 particularly abundant. Compared with levels in normal liver, steatosis had little effect on expression (Fig. 2). In NASH and ALD, the majority of GLUTs were upregulated compared with normal liver. In particular, GLUT1, -3, -5, and -12 were significantly upregulated in disease (Fig. 2). While primary hepatocytes expressed abundant GLUT1, -2, -6, -8, -9, and -10, the hepatocyte cell line Hep G2 showed increased expression of GLUT3, -4, and -8, and BEC showed reduced expression of GLUT8, -9, and -10. Expression of GLUT2 characterized parenchymal cells, since endothelial cells, BEC, and fibroblasts lacked expression (Fig. 3). GLUT5 was only noted on leukocyte populations (peripheral blood mononuclear cells) that lacked GLUT3 expression. Where specific antibodies were available, results were confirmed by immunohistochemical staining (Fig. 4). Representative results for steatotic and NASH livers (Fig. 4) confirm elevated expression of GLUT1, -4, -9, and -10 in chronic disease, but not steatosis, and parenchymal predominance of GLUT2. Disease-matched sections treated with isotype-matched control antibodies were negative (not shown).

We then stained treated human liver tissue slices (PCLS) to visualize localization of receptor expression and see whether the SSAO activity of VAP-1 altered hepatic GLUT expression or localization within human tissue slices. Figure 5A shows that treatment had minimal effects on distribution of GLUT2, whereas GLUT4 was increasingly noted within cytoplasmic vesicles after stimulation (arrowheads in Fig. 5A). In contrast, membranous accumulations of GLUT9 (arrowheads in Fig. 5A) were reduced after treatment, while GLUT10 became more localized to hepatocyte membranes. Fluorescence microscopy confirmed the redistribution of GLUT4 within liver cells following stimulation, and upon activation with ME, we observed...
Fig. 4. Representative immunohistochemical localization of GLUT1, -2, -4, -9, and -10 in normal liver, steatosis, and NASH. Serial sections were stained with isotype-matched control antibodies (not shown). Fields were captured at ×10 or ×40 original magnification and are representative of 3–5 cases for each disease.
increased hepatocyte staining intensity and relocalization into cytoplasmic granules, with a bias toward luminal surfaces of the cell (arrowheads in Fig. 5B). This was not observed in the presence of the VAP-1 inhibitor BEA. Upon activation of hepatic SSAO with MA, we noted upregulation of mRNA for GLUT2, -4, -10, and -13 by qPCR (Fig. 5C).

Next, we used the liver slice model to determine if these changes in GLUT expression and cellular localization had
functional consequences. We previously demonstrated SSAO-dependent NF-κB activation of endothelium with resultant expression of adhesion molecules and cytokines (39). To confirm the functional competence of our human tissue slices ex vivo, we used a human NF-κB PCR array and showed that treatment of human liver slices with H2O2, which is produced by cigarette smoke or amines such as leucine and valine, which are metabolized by the liver (21). The specificity of our responses are used isolated primary HSEC. Glucose uptake by HSEC was stimulated by insulin, as expected, and increased in the presence of MA (Fig. 7B, left), and BEA significantly inhibited the effect of VAP-1 and MA. Responses were variable in primary isolates, so we overexpressed enzymatically active or inactive VAP-1 using adenoviral vectors (43). Glucose uptake in cells transduced with enzymatically capable VAP-1 was twice that of controls (Fig. 7B, right). Finally, we tested whether insulin exposure concurrent with stimulation of VAP-1 had additional effects (Fig. 7C). While we again saw increased glucose uptake in response to insulin and MA, concurrent stimulation of VAP-1 did not enhance insulin-dependent glucose uptake.

**DISCUSSION**

In agreement with our findings, VAP-1 is upregulated in chronically inflamed livers, with increased SSAO activity in chronic liver disease (35). Many patients with cirrhosis, and particularly those with concurrent metabolic syndrome (31), exhibit hepatic insulin resistance (31, 57), deficient hepatic insulin clearance (6), and hyperinsulinemia (31). Glycogen stores are also depleted in cirrhotic livers (60), and collagen accumulation in fibrosis may be associated with reduced accessibility of glucose from blood into tissue (49). Thus the ability of VAP-1 to act independently of insulin and increase glucose uptake is significant and may represent a means to compensate for reduced insulin sensitivity or access to glucose in diseased livers.

VAP-1 is an insulinomimetic (62) that stimulates tyrosine phosphorylation of insulin receptor substrates 1 and 3 and phosphatidylinositol 3-kinase (11). In adipose tissue, VAP-1 drives glucose uptake via H2O2, a metabolite produced during deamination of amines (12). We now report, for the first time, hepatic glucose uptake in response to VAP-1-dependent catalysis of MA. This was due to activation of endogenous VAP-1 within tissue, likely expressed on HSEC, stellate cells, and fibroblastic cells (8, 38). In common with adipose tissue (12), H2O2 recapitulated the response, and increased glucose uptake when exogenous VAP-1 was added alone suggests catalysis of endogenous ligands such as MA, which is found in food and cigarette smoke or amines such as leucine and valine, which are metabolized by the liver (21). The specificity of our responses was confirmed using tissue from VAP-1−/− mice, where MA did not stimulate glucose uptake. However, H2O2-dependent responses in tissue from WT and VAP-1−/− mice confirmed that signaling machinery downstream of VAP-1 was intact in WT and VAP-1−/− animals.

The metabolic responses of VAP-1−/− animals have been widely reported, with particular reference to glucose responses in adipose tissue. VAP-1−/− animals are fatter than WT animals and have more subcutaneous fat pads (5), and they contain more lipid. The animals are normoglycemic, and there is no alteration in glucose tolerance in response to glucose challenge of the animals (5). Thus there is no direct in vivo evidence to suggest that hepatic glucose uptake in VAP-1−/− animals is different from that in WT animals. In VAP-1−/− mice that are engineered to express human VAP-1 only on adipocytes (18), the insulinomimetic effects of VAP-1 substrates are not completely rescued (i.e., glucose uptake remains lower than in WT mice). While this may reflect relative activity levels of human SSAO expressed within murine adipocytes, it also confirms the contribution of extra-adipose VAP-1 to the effect (18). We therefore hypothesize that, in our isolated liver slices, absence of liberated glucose from extrahepatic sources may have a greater effect on liver from VAP-1−/− than WT animals. This may increase the basal glucose requirements of liver slices from VAP-1−/− animals in culture.

![Fig. 6. Human liver slices were treated with methylamine (Ma, 200 μM) + recombinant VAP-1 (500 ng) for −2.5 h. RNA was extracted and mRNA expression was determined using a human NF-κB signaling pathway RT2 Profiler PCR Array. Data represent fold change in gene expression relative to untreated control liver (defined as 1). Values are means ± SE.](http://ajpgi.physiology.org/)
Fig. 7. A: uptake of radiolabeled glucose after stimulation of slices generated from human tissue or mouse liver [wild-type (WT) and VAP-1−/−]. Slices were pretreated with insulin (0.10 IU), methylamine (MA, 200 μM), recombinant VAP-1 (500 ng), H2O2 (10 μM), or BEA (400 μM), alone or in combination, for 2.5 h and for 30 min with radiolabeled glucose. Signal was normalized per 500 mg of tissue. Values are means ± SE; n = 3. Significantly elevated glucose uptake relative to control: *P < 0.05, **P < 0.01, ***P < 0.001 (by ANOVA). B: uptake of radiolabeled glucose after stimulation of HSEC with insulin (0.10 IU), methylamine (200 μM), recombinant VAP-1 (500 ng), or H2O2 (10 μM), alone or in combination, for 2.5 h and for 30 min with radiolabeled glucose (left) and after transfection with enzymatically active VAP-1, inactive construct, or an empty vector containing LacZ (right). Values are means ± SE of 7 (left) or 3 (right) isolates of HSEC from different donors. *P < 0.05, **P < 0.01, ***P < 0.001 (by ANOVA). C: specific uptake of 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (fluorescent deoxyglucose) after stimulation of liver slices with insulin (Ins, 0.10 IU) or methylamine (200 μM), alone or in combination, for 2.5 h. Data represent uptake per 500 mg of tissue where basal uptake in untreated slices was subtracted. Values are means ± SE; n = 6. ANOVA indicated no significant difference between stimulations.
VAP-1 colocalizes in intracellular vesicles with GLUT4 (12), and SSAO-stimulated glucose uptake is based on translocation of GLUT4 (12) or GLUT1 (10) to the cell membrane. Large cytoplasmic GLUT4-containing droplets concentrated toward the periphery of hepatocytes in slices treated with VAP-1 + MA, and we also noted an increase in GLUT4 mRNA following treatment; thus an analogous mechanism may operate in the liver. We report GLUT4 expression in all liver, with protein expression around the endothelium and smooth muscle of vessels, as expected, and cytoplasmic localization in hepatocytes. In agreement with our findings, others have reported decreased hepatic GLUT4 in rodent steatosis (20), which is linked to hepatic insulin resistance (29). Other transporters may also be responsive to signals generated by VAP-1, for example, GLUT8 (7, 53), GLUT10 (42), and GLUT12 (29). Expression of all these GLUTs is increased in NASH and ALD livers, and we saw increased expression of message for GLUT4, -10, and -13 in human tissue following MA treatment. We also noted redistribution of GLUT4 and -10 to hepatocyte membranes and a concurrent cytoplasmic redistribution of GLUT2 and -9. In tissue from human liver diseases associated with hepatic insulin resistance (e.g., nonalcoholic fatty liver disease, ALD, and NASH) (14) and elevated VAP-1 expression, we have demonstrated modifications in GLUT expression compared with normal livers (Fig. 2). Human studies have linked insulin resistance to altered expression of GLUT isoforms by granulosa cells (28) and adipose tissue (33), and rodent livers demonstrate increased GLUT1 and decreased GLUT2 expression when insulin resistance is induced by a high-fat diet (54) or alcohol exposure (48). Induction of experimental diabetes in mice leads to elevated sVAP-1 production (55) in an attempt to improve insulin sensitivity. While our data cannot explicitly link insulin level and GLUT expression, our findings support the hypothesis that, in liver disease, an increase in VAP-1 expression and modification of GLUT expression are concomitant with changes in insulin levels and may represent an attempt to regulate blood glucose levels. As well as changes in GLUT1 and -4, increased expression of GLUT12 may also improve insulin sensitivity and glucose clearance rates in the cirrhotic liver, since overexpression of GLUT12 improves whole body insulin sensitivity and glucose clearance in mice (51). Similarly, while mRNA for GLUT2 was not dramatically altered in liver disease, in two cases of NASH we found diffuse cytoplasmatic staining for GLUT2 with loss of membrane staining, reflecting the situation in treated slices. This response is insulin-dependent in murine hepatocytes (17) and, along with GLUT9, GLUT2 functions as a glucose sensor (15). Our data for diseased liver and MA-treated slices are suggestive of similar insulinoimetic effects of SSAO activity in humans. Enhanced hepatic expression of GLUT10 and -13 induced by MA may also represent a compensatory mechanism to protect against oxidative stress, similar to that of GLUT10 in smooth muscle cells (42). GLUT13, which was upregulated in diseased tissue, can also ameliorate conditions associated with the metabolic syndrome by transporting inositol, which has a role in insulin signaling and as an insulin sensitizer (16). Thus VAP-1 activity has clear metabolic consequences and may counterbalance the effects of insulin resistance and oxidative stress in chronic liver disease. However, it is important to note that VAP-1 can drive tissue inflammation and leukocyte recruitment in the context of disease (39) by regulating expression of ICAM-1 and IL-8 and producing reactive oxygen species as a by-product of its enzymatic capacity. Since we also raise the possibility that activation of protective mechanisms linked to antioxidant responses and hepatic anti-inflammatory gene expression are also induced by VAP-1, it is clear that there is a complex interplay between different aspects of VAP-1 function in disease. Hence, it is important to consider all the possible effects of future therapies directed against VAP-1 (9).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.K., D.H.A., and P.F.L. are responsible for conception and design of the research; S.K., E.L., J.F., A.G., G.R., L.C., and P.F.L. performed the experiments; S.K., E.L., A.G., and P.F.L. analyzed the data; S.K. and P.F.L. interpreted the results of the experiments; S.K. and P.F.L. drafted the manuscript; S.K., E.L., J.F., A.G., D.H.A., P.N.N., and P.F.L. approved the final version of the manuscript; P.N.N. and P.F.L. edited and revised the manuscript; P.F.L. prepared the figures.

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