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Hepatic fuel selection

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Sélection des substrats énergétiques du foie

RÉSUMÉ

Le foie sert d'intermédiaire entre les sources d'énergie alimentaires et extra-hépatiques et les organes extra-hépatiques qui consomment de l'énergie. En pratique, quelque vingt-cinq composés sont soit absorbés, soit fournis en quantités substantielles par le foie. Les glucides, les acides gras libres, l'acétate, les acides aminés et l'éthanol sont des substrats producteurs d'énergie. Le foie utilise de l'énergie pour le transport et les fonctions sécrétoires, la synthèse et le stockage des macromolécules et des substrats énergétiques, les interconversions et le cyclage des substrats. *In vivo*, on peut estimer approximativement la consommation d'O_2 par le foie en mesurant les différences de concentration artério- et porto-hépato-veineuse conjointement avec le flux sanguin dans l'artère hépatique et la veine porte. Chez l'adulte, le foie ne représente que 1·5–2% du poids du corps, mais en même temps assume 20–25% de la dépense d'énergie au repos, ce qui suggère un taux élevé de métabolisme organique (environ 840 kJ/kg de poids organique par jour). 'Etant donné la complexité de l'échange métabolique qui s'opère dans le foie, il est virtuellement impossible de déduire la valeur du mélange énergétique oxydé. Bien que différents flux métaboliques soient bien décrits dans nos ouvrages de référence, le métabolisme hépatique *in vivo* n'a pas été déterminé avec précision. Certains auteurs ont évalué directement. *In vivo* le quotient respiratoire (QR) dans la veine hépatique, citant des valeurs inférieures à 0·70, ce qui suggère une oxydation des graisses et une gluconéogenèse concomitantes dans les conditions basales. Cependant, l'interprétation du 'QR hépatique' est compliquée par des problèmes méthodologiques, par l'interconversion et l'oxydation incomplète des substrats, par le piégeage du CO_2, par une inconnue sur l'oxydation des protéines hépatiques, par la consommation extramitochondriale et par l'hétérogénéité des tissus. On peut aussi mesurer indirectement le 'QR hépatique' en mesurant la consommation d'O_2 hépatique conjointement avec l'échange des métabolites. Cette approche donne une limite supérieure de la contribution de l'oxydation de substrats à la consommation d'O_2 et à la production de CO_2. L'interprétation des données est rendue difficile par des problèmes méthodologiques, des affirmations erronées, le manque de substrats et la mesure de l'oxydation des acides aminés. Dans le jeûne, le 'QR hépatique' estimé varie entre 0·68 et 0·71. Après un repas varié, cette valeur s'élève entre 0·84 et 0·90, ce qui suggére une oxydation concomitante d'acides aminés et de glucides. Si l'on suppose que tout le

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glucose est converti en graisse (ce qui est peu vraisemblable dans la réponse à un repas après le jeûne de la nuit), le 'QR hépatique' peut atteindre 2·1 au maximum. En ce qui concerne les nutriments individuels, ce sont les acides aminés qui exercent l'effet thermique le plus important, alors que les glucides n'augmentent pas la proportion splanchnique de l'augmentation de la consommation d'O_2 du corps tout entier. Ces données suggèrent qu'après un repas la plus grande partie sinon la totalité des glucides est stockée, et l'oxydation hépatique du glucose exogène est négligeable. L'intégrité cellulaire, la disponibilité d'O_2 et de substrats, le flux sanguin hépatique total aussi bien que la proportion de flux sanguin artériel et portal, différentes hormones, le système nerveux autonome et un certain nombre de cytokines, tous ces éléments déterminent la sélection des substrats. Les substrats en provenance du foie à leur tour donnent aux autres tissus le signal d'activer ou d'inhiber les voies d'utilisation ou de production de tel ou tel substrat, affectant à nouveau la fonction métabolique du foie. Ainsi, le foie et les organes extra-hépatiques sont en étroite interaction dans la régulation du métabolisme de tout le corps, en réponse à des facteurs nutritionnels et autres.

ENERGY-PROVIDING AND ENERGY-CONSUMING REACTIONS IN THE LIVER

The liver serves as an intermediary between dietary and endogenous sources of energy and the extrahepatic organs that consume energy. Metabolically the liver is the most versatile organ of the body; about twenty-five compounds are either taken up or released in substantial amounts by the liver. Most of the present knowledge of hepatic fuel metabolism is based on *in vitro* experiments using the isolated perfused rat liver or rat hepatocytes. Normally the liver operates under highly aerobic conditions. Values for hepatic O_2 consumption vary between 2 and 10 μmol/g liver wet weight per min (Berry *et al.* 1973; Krebs *et al.* 1974; Scholz *et al.* 1984; Rabkin & Blum, 1985; Seifter & Englard, 1988). Based on a P:O ratio of 3 (i.e. maximally efficient oxidative phosphorylation) the aerobic ATP supply could be calculated to vary between 12 and 60 μmol/g liver wet weight per min (Krebs *et al.* 1974). Most of the O_2 consumed by the liver is related to mitochondrial metabolism. An additional 0·6–4·5 μmol ATP/g liver wet weight per min may come from anaerobic metabolism of glucose (Krebs *et al.* 1974). Free fatty acids (FFA), pyruvate and amino acids are the preferred fuels of hepatic energy metabolism. Under basal aerobic conditions the liver primarily selects fatty acids as its fuel. If the liver selectively uses fatty acids its theoretical respiratory exchange ratio (RQ) would be 0·71. Ureagenesis, futile cycling of substrates, gluconeogenesis, protein synthesis, Na^+,K^+-ATPase (*EC* 3.6.1.37) and ketogenesis are the main energy-requiring processes in liver metabolism, and their maximum contributions to hepatic O_2 consumption are 35, 22, 19, 11, 6 and 4% respectively (Krebs *et al.* 1974; Jarett *et al.* 1979; Clark *et al.* 1982; Rabkin & Blum, 1985). In the fed state, liver fuel mix changes and amino acids and pyruvate predominate as fuel, whereas most of the carbohydrate is stored as glycogen. At present, the exact contribution of other energy-consuming processes (e.g. hepatic protein degradation or bile acid secretion) to energy expenditure is unknown. *In vitro*, hepatic energy metabolism can be measured under controlled and highly standardized conditions. Cellular integrity and cellular function are well maintained throughout the studies, suggesting near physiological conditions. The drawback of the *in vitro* approach is that the data strongly depend on the experimental conditions (which are

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artificial) and, thus, may not reflect the physiological situation (Davis, 1961; Schwenke *et al.* 1981). *In vitro* studies provide a description of metabolic pathways and their individual capacities, but they cannot provide an integrated view of the physiology and pathophysiology of hepatic metabolism. Obviously, there is a need for *in vivo* assessment of hepatic fuel metabolism.

IN VIVO ASSESSMENT OF HEPATIC FUEL SELECTION

When compared with the abundance of *in vitro* data there is a lack of information on the metabolic rate of the liver *in vivo*. This lack of interest might be explained by the 'approximate' nature of the *in vivo* approach, which cannot give insights into the mechanisms and sites of metabolic regulation. In the intact organism, hepatic O_2 consumption can be estimated, after catheterization, from the arterio– and porto–hepatovenous concentration differences and blood flow in the *arteria hepatica* and the portal vein. In an adult, the liver represents only 15–20 g/kg body weight but accounts for 20–25% of the resting energy expenditure, suggesting a high organ metabolic rate (i.e. about 840 kJ/kg organ weight per d when compared with 54 and 19 kJ/kg organ weight per d in skeletal muscle and subcutaneous adipose tissue respectively; Elia, 1992). Given the complexity of the metabolic exchange occurring in the liver, it is virtually impossible to deduce the oxidized fuel mix *in vivo*. The RQ in the hepatic vein and, thus, the 'splanchnic RQ', which reflects liver plus gut metabolism, has been directly assessed in man (Tygstrup *et al.* 1965; Owen *et al.* 1969; Havel *et al.* 1970; Gil *et al.* 1985). In man, 'splanchnic RQ' (RQ_m) of 0·37 (5–6 weeks of starvation, Owen *et al.* 1969) or 0·18 (overnight fasting, Havel *et al.* 1970) have been measured, suggesting increases in fat oxidation, ketogenesis and gluconeogenesis during overnight or prolonged starvation. Correcting the RQ (RQ_c) for (1) V_{O_2} due to ketogenesis and (2) fixation of CO_2 during urea production, the splanchnic RQ_c became 0·77 and 0·65 respectively. The interpretation of the 'splanchnic RQ' is made difficult by methodological problems (e.g. the measurement of CO_2 content has a CV of 65% in the study of Gil *et al.* 1985), interconversion and incomplete oxidation of substrates, trapping of CO_2 in the tissue bicarbonate pool, or an unknown rate of hepatic protein oxidation during ureagenesis, extramitochondrial O_2 consumption and/or tissue heterogeneity (Frayn *et al.* 1993). Because of these problems the meaning of the 'splanchnic RQ_m' remains obscure. The 'hepatic RQ' or 'splanchnic RQ' can also be assessed indirectly from hepatic O_2 consumption and exchange of metabolites, using the stoichiometry of substrate oxidation (Flatt, 1978, 1992; Frayn, 1983). Measurement of the arterio–venous concentration difference across the liver (or the splanchnic bed) shows whether the tissue(s) takes up or releases metabolites (Elia, 1991). This approach may give an upper limit to the contribution of substrate oxidation to O_2 consumption and CO_2 production. However, if the liver takes up substrates from the circulation, as well as releasing them, the net balance underestimates true uptake. The interpretation of data is made difficult by a number of methodological problems. The arterio–hepatovenous substrate difference is most frequently used instead of the arterial–portal venous–hepatovenous concentration differences (i.e. the 'splanchnic RQ' instead of the 'hepatic RQ'). In addition, the measurement of hepatic blood flow by dye-clearance techniques is not very accurate (i.e. variation of 30%). In addition to the methodological problems, erroneous assumptions (e.g. all substrates come from outside the cell), missing fuel (e.g. an unknown rate of

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intrahepatic glycogen and fat mobilization) and the unknown rate of hepatic amino acid oxidation all limit the value of the indirect assessment of hepatic fuel mix.

HEPATIC FUEL SELECTION IN STARVATION

In starvation, the 'splanchnic RQ' has been directly assessed in subjects fasted for 5–6 weeks and was found to be 0·37, compatible with low CO_2 production in relation to O_2 consumption (Owen *et al.* 1969). These findings suggest increased rates of hepatic gluconeogenesis, fatty acid oxidation and ketogenesis during prolonged starvation. Most studies on hepatic metabolism in fasting man consider splanchnic instead of hepatic balances (Owen *et al.* 1969; Havel, 1974*a*; Dietze *et al.* 1978; Elia, 1991). During short-term starvation (i.e. up to 72 h) hepatic fuel selection was measured in conscious and chronically catheterized miniature pigs (Müller *et al.* 1982, 1983; Table 1). In this study the aorta, the *vena hepatica* and the portal vein were catheterized. In the pig, fasting for 72 h increased hepatic O_2 consumption and glucose output; concomitantly, the rates of urea and ketone-body production as well as amino acid and FFA uptake were all enhanced (Table 1). From the measurement of hepatic exchange of O_2 and metabolites the starvation-induced 'hepatic RQ' was calculated to be 0·68 or 0·71 depending on the assumed unexplained fuel (Table 1). Thus, during tissue catabolism 'liver RQ' is lower than whole-body RQ. In the pig ketogenesis explained up to 28% of hepatic fatty acid metabolism or 22% of hepatic O_2 consumption (Table 1). These values differ from those for humans and rats where hepatic ketone-body production accounts for 37% (after 69 h of starvation in man; Havel, 1974*a*), 72% (after 120 h of starvation in man; Dietze *et al.* 1978) or 68% (after 24 h of starvation in the rat; Remesy & Demigne, 1983) of splanchnic or hepatic FFA uptake. In man, the liver has a high capacity for producing ketone bodies (an estimate of 130–900 g/d has been reported, Reichard *et al.* 1974; McGarry & Foster, 1980) and ketogenesis accounted for up to 50% of hepatic O_2 consumption (Havel, 1974*b*). In the pig, the major enzyme of ketone-body utilization (succinyl-CoA:3-ketoacid-transferase; *EC* 2.8.3.5) could not be detected in the brain, thus, brain glucose consumption could not be replaced by ketone-body utilization (cf. Müller *et al.* 1982). Teleologically, this finding may explain the reduced ketone-body turnover that accompanies increased glucose turnover in pigs. Recalculating the pig data (Table 1) based on the assumption that 60% of hepatic FFA uptake was incompletely oxidized to ketone bodies led to an apparent 'hepatic RQ' of 0·20 after 72 h of starvation. It is evident that during starvation the 'hepatic RQ' does not only depend on fuel supply but results from the rate of hepatic ketogenesis. Since hepatic ketogenesis is not explained only by FFA supply (Keller *et al.* 1988), both substrate supply and the humoral milieu determine hepatic RQ during starvation.

To summarize, during short-term starvation the 'hepatic RQ', estimated from hepatic O_2 consumption and metabolite exchange, varies between 0·20 and 0·71 depending on the rate of ketogenesis. In this situation the 'hepatic RQ' is lower than whole-body RQ.

HEPATIC FUEL SELECTION IN THE POSTPRANDIAL STATE

After a mixed meal, splanchnic O_2 consumption increased (Brundin *et al.* 1992; Brundin, 1993). The splanchnic-related proportion of the rise in whole-body O_2 consumption in the 2 h after a mixed meal, a carbohydrate meal containing fructose or glucose, a protein

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Table 1. *Hepatic substrate metabolism and energy balance during metabolic adaptation to starvation as measured in the conscious unrestrained miniature pig* (From Müller *et al.* 1982, 1983)

(Mean values and standard deviations for four to seven pigs; body wt 21 kg; liver wt:body wt 24 g/kg)

Starvation period (h) . . .	0		24		72	
	Mean	SD	Mean	SD	Mean	SD
Blood flow (ml/kg body wt per min)	38·2	2·3	42·6	6·5	43·6	5·9
O_2 consumption (μmol/kg body wt per min)	41·6	3·6	56·1	3·8	53·3	6·6
Substrate and energy balance (μmol/kg body wt per min)						
Glucose	+9·1	3·0	+24·0	6·7	+20·5	3·4
Alanine → glucose*	0		+14·7	2·3	8·5	2·1
CO_2 used for urea production			−7·4		−4·3	
V_{O_2} correction for pyruvate production	0·2		0		0	
Lactate	−5·9	3·6	−10·0	3·1	−6·5	0·8
Lactate → CO_2†	3·0		2·0		0·7	
V_{O_2}	9·0		6·0		2·1	
V_{CO_2}‡	6·0		4·0		1·4	
Free fatty acids	+0·1	0·0	−2·1	0·8	−6·3	2·1
Ketone bodies	+0·3	0·1	+4·2	1·7	+7·2	3·2
βHOB:AcAc§	1·90		1·25		1·58	
Free fatty acids→:Ketone bodies‖	0		1·1		1·8	
CO_2¶	0		1·0		0·7	
V_{O_2}	0		23·6		16·4	
V_{CO_2}	0		16·4		11·4	
V_{O_2} due to: AcAc produced**	0		4·4		10·3	
βHOB produced**	0		2·1		1·6	
Amino acids††	−49·6	14·2	−18·4	5·8	−11·3	3·7
Urea	+2·3	2·9	+4·5	0·6	+5·2	1·3
Amino acids→:Urea	4·6		9·0		10·4	
CO_2‡‡	3·2		2·7		3·1	
V_{O_2}	16·3		13·8		15·8	
V_{CO_2}	13·1		11·1		12·7	
CO_2 used for urea production	2·3		4·5		5·2	
Unexplained fuel§§‖‖	16·1		6·2		7·1	
Fuel mix (%):						
Carbohydrates	62§§, 41‖‖		22§§, 14‖‖		17§§, 6‖‖	
Lipids	0§§, 20‖‖		54§§, 61‖‖		53§§, 64‖‖	
Amino acids	39§§, 39‖‖		25§§, 25‖‖		30§§, 30‖‖	
Apparent 'tissue' RQ	0·90§§, 0·84‖‖		0·75§§, 0·73‖‖		0·71§§, 0·68‖‖	

βHOB, β-hydroxybutyrate; AcAc, acetoacetate.

* Assuming a maximum conversion efficiency, i.e. all alanine is converted to glucose.

† Assuming that 50 (0 h) or 20% (24 and 72 h) of the extracted lactate is oxidized.

‡ After correction for possible CO_2 retention in the tissue bicarbonate pool because of H^+ production.

§ As calculated from the hepatovenous substrate concentrations.

‖ As calculated from hepatic free fatty acid extraction and ketone-body production assuming a fatty acid chain length of C_{18}.

¶ As calculated from the difference between hepatic oxygen consumption minus V_{O_2} due to carbohydrate and amino acid oxidation plus incomplete oxidation of free fatty acids to ketone bodies.

** Assuming 1·75 mol O_2 consumed/mol AcAc produced and 1·25 mol O_2 consumed/mol βHOB produced. The calculation is based on the hepatic production rate of the individual ketone bodies.

†† As calculated from the net balance of α-amino-N.

‡‡ As calculated from the urea production rate assuming that 70 (0 h) or 30% (24 and 72 h) of the amino acid-C skeleton is directly oxidized.

§§ Unexplained fuel is explained as glucose oxidation.

‖‖ Unexplained fuel is explained as 50% glucose and 50% lipid oxidation derived from hepatic energy stores (0 h), or 30%:70% (24 h) and 15%:85% (72 h) respectively.

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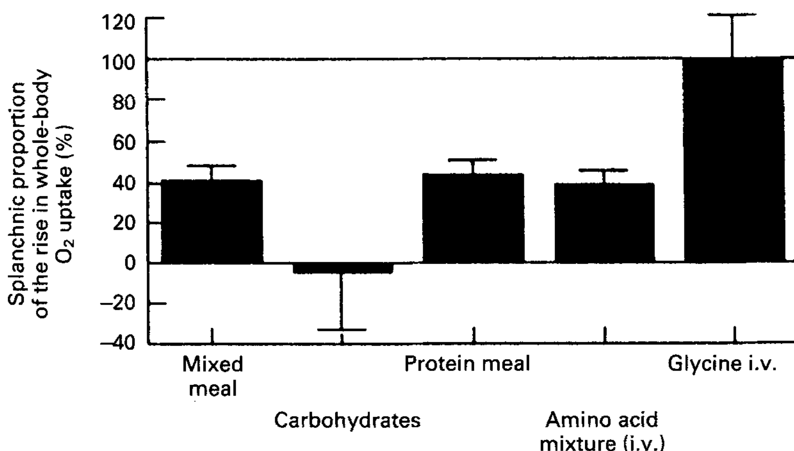

Fig. 1. Splanchnic proportion of the rise in whole-body O_2 consumption in the 2 h after a mixed meal containing 40% of basal energy requirements. Carbohydrate meals contained 75 g fructose or glucose. The protein meal contained 900 kJ fish meat. Amino acids were infused at a rate of 240 kJ/h. A mixture of nineteen amino acids or glycine alone was infused intravenously (i.v.). Experiments were performed on thirty-four healthy normal weight men. Values are means with their standard errors represented by vertical bars. (Data from Brundin (1993); reproduced with kind permission of Professor John Wahren.)

meal or after intravenous infusion of amino acids is shown in Fig. 1 (Brundin & Wahren, 1993, 1994). The findings suggest that the postprandial rise in splanchnic O_2 consumption was substrate specific. Amino acids had a strong thermic effect on hepatic metabolism, whereas exogenous carbohydrates were mostly stored postprandially. The latter idea is supported by several lines of evidence. First, the postprandial hepatic glycogen synthesis accounts for 20–30% of an oral glucose load (i.e. 15–30 g; Kelley *et al.* 1988; Radziuk, 1989). In humans, hepatic glycogen content is about 70–100 g (i.e. about 7–10% of liver wet weight) with a turnover of about 47 g/d (Rothman *et al.* 1991; Gay *et al.* 1994). This value is in line with the minimal estimate of the proportion of oral glucose taken up by the splanchnic bed (i.e. 25–30%; Jackson *et al.* 1983; Ferrannini *et al.* 1985; Kelley *et al.* 1988). Second, at the whole-body level 30–40% of the oral glucose was oxidized directly in brain, heart and skeletal muscle (Ebiner *et al.* 1979; Kelley *et al.* 1988), leaving only 1–2% of the oral glucose for oxidation in splanchnic and other tissues. This is in line with the finding that up to 4% of an oral glucose load is oxidized within the splanchnic area (Abumrad *et al.* 1982). Third, since hepatic glycogen synthesis and degradation are active simultaneously in fed and fasted rats and humans (David *et al.* 1990; Magnusson *et al.* 1994), glucose oxidation may occur after mobilization of glycogen. In man, minimum estimates of the relative liver glycogen turnover were 31% in the fasted state and 57% in the fed state (Magnusson *et al.* 1994). In the fed state the flux through glycogen synthase (*EC* 2.4.1.11) was 0·53 μmol/ml liver per min and glycogen breakdown was calculated to be 0·30 μmol/ml liver per min (Magnusson *et al.* 1994). After a glucose load hepatic glucose output decreased from 11·1 to 4·4 μmol/kg body weight per min (Kelley *et al.* 1988). Assuming that hepatic glycogen breakdown was unchanged in the fed state, hepatic glucose oxidation from endogenous sources could reach a maximum of 6·7 μmol/kg body weight per min. This value is close to the estimated rate of hepatic

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glycogenolysis based on experiments using liver-biopsy techniques (i.e. 6·9 μmol/kg body weight per min or 0·32 μmol/g liver per min; Nilsson *et al.* 1973) and ^{13}C NMR studies. The importance of net hepatic lipogenesis is less evident in man. It is unlikely that quantitatively significant lipogenesis occurs when a carbohydrate load is preceded by overnight fasting (Hellerstein *et al.* 1991, 1993); in non-obese, non-diabetic and non-overfed healthy subjects only about 1 g fat was synthesized in response to a variety of feeding regimens (Hellerstein *et al.* 1991). Lipogenesis remains low in subjects overfed carbohydrates in a mixed diet (Thomas *et al.* 1992). Substantial lipogenesis occurs after hepatic glycogen stores are fully saturated by massive intakes of glucose (for example, 500 g glucose; Acheson *et al.* 1988).

The present evidence suggests that after a meal most, if not all, carbohydrate is stored as glycogen, and hepatic oxidation of exogenous glucose and hepatic lipogenesis are negligible. Postprandially, hepatic RQ increases to 0·84–0·90, suggesting concomitant amino acid and carbohydrate oxidation (Table 1). Assuming that 50% of the missing fuel is explained by O_2 consumption due to lipogenesis an RQ of 1·04 can be calculated. If all the glucose is converted to fat (which is unlikely in response to a meal after an overnight fast) hepatic RQ can reach 2·1. Of the individual nutrients amino acids exert the strongest thermic effect. During tissue anabolism 'splanchnic RQ' may equal or exceed 'whole-body RQ'.

HEPATIC FUEL SELECTION DURING EXERCISE

During exercise the liver provides substrates (1) to maintain fuel homeostasis (i.e. to maintain euglycaemia), (2) to meet muscle energy demands and (3) to conserve C as well as N (Wasserman & Cherrington, 1991). While muscle glycogen provides the first source of energy, liver fuel production becomes of increasing importance with increasing duration of exercise. Splanchnic blood flow decreases in response to heavy exercise (i.e. 55–60% of V_{O_2max} for 40 min; Wahren *et al.* 1975). Concomitantly, O_2 and lactate uptake, gluconeogenesis, glycogenolysis and hepatic output of glucose all increase, whereas total amino acid balance across the splanchnic bed decreases. Splanchnic glucose output increases two- to fivefold, depending on the intensity of the work performed (Felig & Wahren, 1975). In healthy subjects, the splanchnic balances of FFA and ketone bodies are unaltered or decreased in response to exercise (Hagenfeldt & Wahren, 1973; Wahren *et al.* 1975). However, hepatic FFA uptake and ketogenesis increase with prolonged exercise (Wasserman & Cherrington, 1991). Assuming an hepatic glycogen breakdown of 2·50 mmol/min, which adds to plasma substrates as an energy fuel, an apparent splanchnic RQ of 0·88 was calculated during heavy exercise. During moderate and prolonged exercise (30% V_{O_2max}, 4 h) splanchnic O_2 consumption and the uptakes of lactate, FFA and amino acids all increase but glycogen stores decrease (Ahlborg *et al.* 1974; Wasserman & Cherrington, 1991). This is associated with an increase in gluconeogenesis, splanchnic glucose output, fat oxidation and ketogenesis. Splanchnic glucose output increases twofold in 40 min and remains constant thereafter (Felig & Wahren, 1975). In addition to hepatic FFA uptake, the mobilization of intrahepatic fat stores may also add to hepatic fat oxidation and ketogenesis. During prolonged exercise hepatic ketogenic efficiency may reach 40% of hepatic FFA uptake (Wasserman & Cherrington, 1991). Assuming a ketone-body production of 0·22 mmol/min (Wasserman & Cherrington, 1991), after prolonged exercise a splanchnic RQ

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of 0·65 can be calculated. Thus, during prolonged exercise 'splanchnic RQ' is lower than 'whole-body RQ'.

HEPATIC FUEL SELECTION IN LIVER CIRRHOSIS

In cirrhosis, basal splanchnic O_2 consumption was variable, but lower-than-normal mean values were found in groups of patients (Merli *et al.* 1986; Bahr, 1994; Müller *et al.* 1994*a*,*b*). Postabsorptive splanchnic glucose output also was highly variable and mean values were low (Owen *et al.* 1981, 1985; Nosadini *et al.* 1984; Merli *et al.* 1986; Bahr, 1994; Müller *et al.* 1994*b*). Both reduced gluconeogenesis and reduced glycogen concentrations add to reduced hepatic glucose output in cirrhotic patients. Splanchnic uptake of FFA was normal or increased (Owen *et al.* 1981; Merli *et al.* 1986; Bahr, 1994). Reported values for cirrhotic patients range from lower to higher than normal (Owen *et al.* 1981; Nosadini *et al.* 1984; Merli *et al.* 1986; Müller *et al.* 1994*b*). The rate of ketone-body production in response to increased FFA supply was reduced suggesting impaired ketogenesis in cirrhosis (Müller *et al.* 1992). Urea production rate was highly variable in cirrhosis, but normal mean values were found in groups of patients (Owen *et al.* 1981; Merli *et al.* 1986; Bahr, 1994). The calculation of the 'splanchnic RQ', based on the data of Merli *et al.* (1986), led to a value of 0·55 in cirrhosis when compared with 0·69 in healthy controls. The low 'hepatic RQ' suggests tissue catabolism, and is in line with hepatic glucose oxidation limited by reduced glycogen stores (Owen *et al.* 1981, 1983). In cirrhosis, the 'hepatic RQ' is less than the low 'whole-body RQ' reflecting hepatic as well as whole-body tissue catabolism.

DETERMINANTS OF HEPATIC FUEL SELECTION

Liver fuel selection is tightly controlled by a number of different factors. The substrates coming from the liver are signals to other tissues (e.g. skeletal muscle) to activate or inhibit pathways of utilization or production of one fuel or another, thereby affecting the metabolic function of the liver. Thus, the liver and extrahepatic organs closely interact in the regulation of whole-body metabolism in response to nutritional and other factors (Elia, 1991). Cellular integrity, O_2 and substrate supply, total hepatic blood flow as well as the proportion of arterial and portal blood flow, local mediators, hormones (insulin, glucagon, growth hormone, thyroid hormones, cortisol), the autonomic nervous system, metabolic factors (FFA, glucose) and a number of cytokines (tumour necrosis factor α, interleukins 1 and 6, transforming growth factor β, epidermal growth factor, insulin-like growth factor; Andus *et al.* 1991) all determine hepatic fuel selection. In some physiological situations, substrate supply is an important determinant of liver metabolism and may become rate-limiting. In starvation, the increased endogenous substrate (FFA) supply, metabolic factors (increase in plasma FFA at decreased glucose concentrations) and the alterations in the humoral milieu (fall in plasma insulin levels, a decreased activity of the sympathetic nervous system at concomitantly increased plasma glucagon concentrations) together explain hepatic fuel selection. In the postprandial state, increased splanchnic perfusion, the portal venous substrate concentration (e.g. hyperglycaemia in the portal blood; Adkins *et al.* 1987), the fall in the glucagon:insulin ratio and FFA levels in the portal blood all determine hepatic fuel metabolism. In the well-insulinized state hyperglycaemia inhibits hepatic glucose production and, thus,

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alters hepatic energy demands (Müller *et al.* 1988, 1990). In addition, the postprandial activation of the sympathetic nervous system favours hepatic energy flux and tissue anabolism. During exercise splanchnic circulation decreases but endogenous substrate supply increases. Concurrently, FFA, glucagon and the sympathetic nervous system stimulate liver metabolism in order to meet the energy demands of the extrahepatic tissues. During moderate exercise hepatic fuel metabolism was related primarily to the glucagon:insulin ratio rather than the fall in insulin secretion alone (Wasserman & Cherrington, 1991; Vranic, 1992). Together the two hormones control almost 100% of hepatic glucose production (Wasserman & Cherrington, 1991). During prolonged exercise FFA become more important both as a fuel and as determinants of increased gluconeogenesis: FFA delivery to the liver, FFA uptake and hepatic oxidation as well as ketogenesis are all increased. Increased FFA oxidation increased hepatic gluconeogenesis (Yamatani *et al.* 1992). During intense exercise catecholamines become major regulators. In cirrhosis, splanchnic circulation is more or less disturbed and there is a loss in cellular integrity and liver function. The present evidence suggests that the physiological factors regulating hepatic fuel metabolism become less important in the cirrhotic liver. In acute liver disease, prostaglandins and cytokines produced locally and/or systemically may exert profound effects on liver metabolism. Their exact contribution is presently unknown.

CONCLUSION

Although hepatic intermediary metabolism is well characterized by numerous *in vitro* studies there are only a few *in vivo* data on hepatic fuel selection. Since *in vitro* experiments may not reflect the physiological situation, there is a need for *in vivo* studies. In the liver, the direct and indirect assessments of metabolic functions are limited by certain methodological problems. As a consequence the present evidence is based on a number of assumptions which have to be proven in future studies. The liver is responsible for 20–30% of whole-body energy expenditure. Hepatic fuel selection can change considerably in different circumstances. During catabolism the 'hepatic RQ' is lower than the whole-body RQ. By contrast, the hepatic RQ may exceed whole-body RQ during extreme anabolism (i.e. after full repletion of hepatic glycogen stores and significant lipogenesis). Amino acids exert a strong thermic effect on liver metabolism, whereas exogenous carbohydrate is stored and does not meet directly hepatic energy demands. Several determinants integrate hepatic metabolism into whole-body metabolism. The individual determinants of hepatic fuel selection are of varying importance during different physiological and pathophysiological situations. Physiological determinants of hepatic metabolism become secondary in liver cirrhosis, where disturbances in splanchnic haemodynamics and the loss in cellular integrity are the predominant factors.

REFERENCES

Abumrad, N. N., Cherrington, A. D., Williams, P. E., Lacy, W. W. & Rabin, D. (1982). Adsorption and disposition of a glucose load in the conscious dog. *American Journal of Physiology* **242,** E398–E406.

Acheson, K., Schutz, Y., Bessard, T., Anantharaman, K., Flatt, J. P. & Jequier, E. (1988). Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. *American Journal of Clinical Nutrition* **48,** 240–247.

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Adkins, B. A., Myers, S. R., Hendrick, G. K., Stevenson, R. W., Williams, P. E. & Cherrington, A. D. (1987). Importance of the rate of intravenous glucose delivery to hepatic glucose balance in the conscious dog. *Journal of Clinical Investigation* **79,** 557–565.

Ahlborg, G., Felig, P., Hagenfeldt, L., Hendler, R. & Wahren, J. (1974). Substrate turnover during prolonged exercise. *Journal of Clinical Investigation* **53,** 1080–1090.

Andus, T., Bauer, J. & Gerok, W. (1991). Effects of cytokines on the liver. *Hepatology* **13,** 364–375.

Bahr, M. (1994). Energiestoffwechsel und hepatische Haemodynamik bei Patienten mit Leberzirrhose (Energy expenditure and splanchnic haemodynamics in patients with liver cirrhosis). Doctoral Thesis, Medizinische Hochschule Hannover, Hannover.

Berry, M. N., Kun, E. & Werner, H. V. (1973). Regulatory role of reducing equivalent transfer from substrate to oxygen in the hepatic metabolism of glycerol and sorbitol. *European Journal of Biochemistry* **33,** 407–417.

Brundin, T. (1993). Mechanisms of nutrient-induced thermogenesis: total and splanchnic oxygen consumption and blood flow. *International Journal of Obesity*, Suppl. 3, S52–S55.

Brundin, T., Thörne, A. & Wahren, J. (1992). Heat leakage across the abdominal wall and meal-induced thermogenesis in normal-weight and obese subjects. *Metabolism* **41,** 49–55.

Brundin, T. & Wahren, J. (1993). Whole body and splanchnic oxygen consumption and blood flow after oral ingestion of fructose or glucose. *American Journal of Physiology* **264,** E504–E513.

Brundin, T. & Wahren, J. (1994). Effects of i.v. amino acids on human splanchnic and whole body oxygen consumption, blood flow and blood temperatures. *American Journal of Physiology* **266,** E396–E402.

Clark, D. G., Brinkman, M., Filsell, O. H., Lewis, S. J. & Berry, M. N. (1982). No major role for (Na^+K^+)-dependent adenosine triphosphatase apparent in hepatocytes from hyperthyroid rats. *Biochemical Journal* **202,** 661–665.

David, M., Petit, W. A., Laughlin, M. R., Shulman, R., King, J. E. & Barrett, E. J. (1990). Simultaneous synthesis and degradation of rat liver glycogen. An in vitro nuclear magnetic resonance spectroscopic study. *Journal of Clinical Investigation* **86,** 612–617.

Davies, M. (1961). On body size and tissue respiration. *Journal of Cellular and Comparative Physiology* **57,** 135–147.

Dietze, G., Wicklmayr, M. & Mehnert, H. (1978). On the key role of ketogenesis for the regulation of glucose homoeostasis during fasting: Intrahepatic control, ketone levels and peripheral pyruvate oxidation. In *Biochemical and Clinical Aspects of Ketone Body Metabolism*, pp. 213–225 [H. D. Söling and C. D. Seufert, editors]. Stuttgart: G. Thieme Publisher.

Ebiner, J. R., Acheson, K. J., Doerner, A., Maeder, E., Arnaud, M. J., Jequier, E. & Felber, J. P. (1979). Comparison of carbohydrate utilization in man using indirect calorimetry and mass spectrometry after an oral load of 100 g naturally labelled [^{13}C]glucose. *British Journal of Nutrition* **41,** 419–429.

Elia, M. (1991). The inter-organ flux of substrates in fed and fasted man, as indicated by arterio–venous balance studies. *Nutrition Research Reviews* **4,** 3–31.

Elia, M. (1992). Organ and tissue contribution to metabolic rate. In *Energy Metabolism: Tissue Determinants and Cellular Corollaries*, pp. 61–80 [J. M. Kinney and H. N. Tucker, editors]. New York: Raven Press Ltd.

Felig, P. & Wahren, J. (1975). Fuel homeostasis in exercise. *New England Journal of Medicine* **293,** 1078–1084.

Ferrannini, E., Bjorkman, O., Reichard, G., Pilo, A., Olsson, M., Wahren, J. & DeFronzo, R. (1985). The disposal of an oral glucose load in healthy subjects: a quantitative study. *Diabetes* **34,** 580–588.

Flatt, J. P. (1978). The biochemistry of energy expenditure. In *Recent Advances in Obesity Research*, vol. 2, pp. 211–218 [G. Bray, editor]. London: Newman Publishing.

Flatt, J. P. (1992). Energy costs for ATP synthesis. In *Energy Metabolism: Tissue Determinants and Cellular Corollaries*, pp. 319–342 [J. M. Kinney and H. N. Tucker, editors]. New York: Raven Press Ltd.

Frayn, K. N. (1983). Calculation of substrate oxidation rates in vivo from gaseous exchange. *Journal of Applied Physiology* **55,** 628–634.

Frayn, K. N., Lund, P. & Walker, M. (1993). Interpretation of oxygen and carbon dioxide exchange across tissue beds in vivo. *Clinical Science* **85,** 373–384.

Gay, L. J., Schneiter, Ph., Schutz, Y., Di Vetta, V., Jequier, E. & Tappy, L. (1994). A non-invasive assessment of hepatic glycogen kinetics and post-absorptive gluconeogenesis in man. *Diabetologia* **37,** 517–523.

Gil, K. M., Gump, F. E., Starker, P. M., Askanazy, J., Elwyn, D. H. & Kinney, J. M. (1985). Splanchnic substrate balance in malnourished patients during parenteral nutrition. *American Journal of Physiology* **248,** E409–E419.

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Hagenfeldt, L. & Wahren, J. (1973). Effect of exercise on splanchnic exchange of free fatty acids. *Metabolism* **22,** 815–820.

Havel, R. J. (1974*a*). Interrelationship between carbohydrate and lipid metabolism in the splanchnic region in man. In *Regulation of Hepatic Metabolism*, pp. 180–190 [F. Lundquist and N. Tygstrup, editors]. Copenhagen: Munksgaard.

Havel, R. J. (1974*b*). Splanchnic and extrasplanchnic use of fuels in man. In *Regulation of Hepatic Metabolism*, pp. 612–616 [F. Lundquist and N. Tygstrup, editors]. Copenhagen: Munksgaard.

Havel, R. J., Kane, J. P., Balasse, E. O., Segel, N. & Basso, L. V. (1970). Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans. *Journal of Clinical Investigation* **49,** 2017–2035.

Hellerstein, M. K., Christiansen, M., Kaempfer, S., Kletke, C., Wu, K., Reid, J. S., Hellerstein, S. & Shackleton, C. H. L. (1991). Measurement of de novo hepatic lipogenesis in humans using stable isotopes. *Journal of Clinical Investigation* **87,** 1841–1852.

Hellerstein, M. K., Neese, R. A. & Schwarz, J.-M. (1993). Model for measuring absolute rates of hepatic de novo lipogenesis and reesterification of free fatty acids. *American Journal of Physiology* **265,** E814–E820.

Jackson, R., Blix, P., Matthews, J., Morgan, L., Rubenstein, A. & Nabarro, J. (1993). Comparison of peripheral glucose uptake after oral glucose loading and a mixed meal. *Metabolism* **32,** 706–710.

Jarrett, I. G., Clark, D. G., Filsell, O. H., Harvey, J. W. & Clark, M. G. (1979). The application of microcalorimetry to the assessment of metabolic efficiency in isolated rat hepatocytes. *Biochemical Journal* **180,** 631–638.

Keller, U., Gerber, P. P. G. & Stauffacher, W. (1988). Fatty acid-independent inhibition of hepatic ketone body production by insulin in humans. *American Journal of Physiology* **254,** E694–E699.

Kelley, D., Mitrakou, A., Marsh, H., Schwenk, F., Benn, J., Sonnenberg, G., Arcangeli, M., Aoki, T., Sorensen, J., Berger, M., Sonksen, P. & Gerich, J. (1988). Skeletal muscle glycolysis, oxidation and storage of an oral glucose load. *Journal of Clinical Investigation* **81,** 1563–1571.

Krebs, H. A., Cornell, N. W., Lund, P. & Hems, R. (1974). Some aspects of hepatic energy metabolism. In *Regulation of Hepatic Metabolism*, pp. 549–565 [F. Lundquist and N. Tygstrup, editors]. Copenhagen: Munksgaard.

McGarry, J. D. & Foster, D. W. (1980). Regulation of free fatty acid oxidation and ketone body production. *Annual Review of Biochemistry* **49,** 395–420.

Magnusson, I., Rothman, D. L., Jucker, B., Cline, G. W., Shulman, R. G. & Shulman, G. I. (1994). Liver glycogen in fed and fasted humans. *American Journal of Physiology* **266,** E796–E803.

Merli, M., Eriksson, L. S., Hagenfeldt, L. & Wahren, J. (1986). Splanchnic and leg exchange of free fatty acids in patients with cirrhosis. *Journal of Hepatology* **3,** 348–355.

Müller, M. J., Acheson, K. J., Burger, A. G. & Jequier, E. (1990). Evidence that hyperglycemia per se does not inhibit hepatic glucose production in man. *European Journal of Applied Physiology* **60,** 293–299.

Müller, M. J., Böker, K. H. W. & Selberg, O. (1994*a*). Are patients with liver cirrhosis hypermetabolic? *Clinical Nutrition* **13,** 131–144.

Müller, M. J., Böker, K. H. W. & Selberg, O. (1994*b*). Metabolism of energy yielding substrates in liver cirrhosis. *Clinical Investigator* (In the Press).

Müller, M. J., Möhring, J. & Seitz, H. J. (1988). Regulation of hepatic glucose output by glucose in vivo. *Metabolism* **37,** 55–60.

Müller, M. J., Paschen, U. & Seitz, H. J. (1982). Starvation-induced ketone body production in the conscious unrestrained miniature pig. *Journal of Nutrition* **112,** 1379–1386.

Müller, M. J., Paschen, U. & Seitz, H. J. (1983). Glucose production measured by tracer and balance data in conscious miniature pig. *American Journal of Physiology* **244,** E236–E244.

Müller, M. J., Rieger, A., Willmann, O., Lautz, H. U., Balks, H. J., von zur Mühlen, A., Canzler, H. & Schmidt, F. W. (1992). Metabolic responses to lipid infusions in patients with liver cirrhosis. *Clinical Nutrition* **11,** 193–206.

Nilsson, L. H., Fürst, P. & Hultman, E. (1973). Carbohydrate metabolism of the liver in normal man under varying dietary conditions. *Scandinavian Journal of Clinical and Laboratory Investigation* **32,** 331–337.

Nosadini, R., Avogadro, A., Mollo, F., Marescotti, C., Tiengo, A., Duner, E., Merkel, C., Gatta, A., Zuin, R., DeKreutzenberg, S., Trevisan, T. & Crepaldi, G. (1984). Carbohydrate and lipid metabolism in cirrhosis. Evidence that hepatic uptake of gluconeogenic precursors and of free fatty acids depends on effective hepatic blood flow. *Journal of Clinical Endocrinology and Metabolism* **58,** 1125–1132.

Owen, O. E., Felig, P., Morgan, A. P., Wahren, J. & Cahill, G. F. Jr (1969). Liver and kidney metabolism during prolonged starvation. *Journal of Clinical Investigation* **48,** 574–583.

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Owen, O. E., Mozzoli, M. A., Reichle, F. A., Kreulen, T. H., Owen, R. S., Boden, G. & Polansky, M. (1985). Hepatic and renal metabolism before and after portasystemic shunts in patients with cirrhosis. *Journal of Clinical Investigation* **76**, 1209–1217.

Owen, O. E., Reichle, F. A., Mozzoli, M. A., Kreulen, T., Patel, M. S., Elfenbein, I. B., Golsorkhi, M., Chang, K. H. Y., Rao, N. S., Sue, H. S. & Boden, G. (1981). Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis. *Journal of Clinical Investigation* **68**, 240–252.

Owen, O. E., Trapp, V., Reichard, G. Jr, Mozzoli, M. A., Moctezuma, J., Paul, P., Scutches, G. L. & Boden, G. (1983). Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. *Journal of Clinical Investigation* **72**, 1821–1832.

Rabkin, M. & Blum, J. J. (1985). Quantitative analysis of intermediary metabolism in hepatocytes incubated in the presence and absence of glucagon with a substrate mixture containing glucose, ribose, fructose, alanine and acetate. *Biochemical Journal* **225**, 761–786.

Radziuk, J. (1989). Hepatic glycogen in humans. I. Direct formation after oral or intravenous glucose or after a 24-h fast. *American Journal of Physiology* **257**, E145–E157.

Reichard, G. A., Owen, O. E., Haff, A. C., Paul, B. & Bortz, W. M. (1974). Ketone body production and oxidation in fasting obese humans. *Journal of Clinical Investigation* **53**, 508–515.

Remesy, C. & Demigne, C. (1983). Changes in the availability of glucogenic and ketogenic substrates and liver metabolism in fed or starved rats. *Annals of Nutrition and Metabolism* **27**, 57–70.

Rothman, D. L., Magnusson, I., Katz, L. D., Shulman, R. G. & Shulman, G. I. (1991). Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with ^{13}C NMR. *Science* **254**, 573–576.

Scholz, R., Schwabe, U. & Soboll, S. (1984). Influence of fatty acids on energy metabolism. 1. Stimulation of oxygen consumption, ketogenesis, and CO_2-production following addition of octanoate and oleate in perfused rat liver. *European Journal of Biochemistry* **141**, 223–230.

Schwenke, W.-D., Soboll, S., Seitz, H. J. & Sies, H. (1981). Mitochondrial and cytosolic ATP/ADP ratios in rat liver in vivo. *Biochemical Journal* **200**, 405–408.

Seifter, S. & Englard, S. (1988). Energy metabolism. In *The Liver: Biology and Pathobiology*, 2nd ed., pp. 279–315 [J. M. Arias, W. B. Jacoby, H. Popper, D. Schachter and D. A. Shafritz, editors]. New York: Raven Press Ltd.

Thomas, C. D., Peters, J. C., Reed, G. W., Abumrad, N. N., Sun, M. & Hill, J. O. (1992). Nutrient balance and energy expenditure during ad libitum feeding of high-fat and high-carbohydrate diets in humans. *American Journal of Clinical Nutrition* **55**, 934–942.

Tygstrup, N., Winkler, K. & Lundquist, F. (1965). The mechanism of the fructose effect on the ethanol metabolism of the human liver. *Journal of Clinical Investigation* **44**, 817–830.

Vranic, M. (1992). Banting Lecture: Glucose turnover. A key to understanding the pathogenesis of diabetes (indirect effects of insulin). *Diabetes* **41**, 1188–1206.

Wahren, J., Hagenfeldt, L. & Felig, P. (1975). Splanchnic and leg exchange of glucose, amino acids and free fatty acids during exercise in diabetes mellitus. *Journal of Clinical Investigation* **55**, 1303–1314.

Wasserman, D. H. & Cherrington, A. D. (1991). Hepatic fuel metabolism during muscular work: role and regulation. *American Journal of Physiology* **260**, E811–E824.

Yamatani, K., Quing Shi, Z., Giacca, A., Gupta, R., Fisher, S., Lickley, H. L. A. & Vranic, M. (1992). Role of FFA–glucose cycle in glucoregulation during exercise in total absence of insulin. *American Journal of Physiology* **263**, E646–E653.

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