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in

Priolo A. (ed.), Biondi L. (ed.), Ben Salem H. (ed.), Morand-Fehr P. (ed.).
Advanced nutrition and feeding strategies to improve sheep and goat

Zaragoza : CIHEAM
Options Méditerranéennes : Série A. Séminaires Méditerranéens; n. 74

2007
pages 435-440

Regulation of hepatic blood flow by feeding conditions in sheep: A meta-analysis

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SUMMARY – The relationships between hepatic blood flows and dietary intakes by sheep were evaluated by meta-analysis of published data. The influence of dry matter intake (DMI) and of metabolisable energy intake (MEI) were quantified after selection of the publications that presented sufficient variations in the independent variables. In fed sheep, increments of 1 g DMI /(d.kg BW) increased blood flows by 61, 20 and 81 ml/(h.kg BW) in portal vein, hepatic artery and hepatic vein, respectively and increments of 1 kJ MEI/(d.kg BW) increased flow by 5.7, 2.0 and 7.8 ml/(h.kg BW), in the respective vessels (P<0.01). In fasted *vs* fed sheep, the response was lower. The contribution of hepatic arterial to total hepatic blood flow was independent of both fasting and feeding level.

Keywords: Hepatic blood flow, metabolisable energy, intake, sheep, meta-analysis.

RESUME – *"Régulation du débit sanguin hépatique des ovins par les conditions alimentaires : une méta-analyse". Les relations entre les débits sanguins hépatiques et les quantités ingérées par des moutons ont été évaluées par méta-analyse de données publiées. L'influence des quantités de matière sèche et d'énergie métabolisable ingérées (MSI, MEI) a été quantifiée après sélection des publications qui présentaient des variations suffisantes sur les variables indépendantes. Chez les moutons alimentés, des augmentations de 1 g MSI/(j.kg PV) ont entraîné une augmentation des débits sanguins de 61, 20 et 81 ml/(h.kg PV) en veine porte, artère hépatique et veine sus-hépatique, respectivement. L'augmentation de 1 kJ EMI/(j.kg PV) a entraîné une augmentation des débits de 5,7, 2,0 et 7,8 ml/(h.kg PV), dans les mêmes vaisseaux (P<0,01). Chez les moutons à jeun* vs *alimentés la réponse était inférieure. La contribution du débit sanguin hépatique artériel au débit sanguin hépatique total était indépendante à la fois du jeûne et du niveau d'alimentation.*

Mots-clés : *Débit sanguin hépatique, énergie métabolisable, ingéré, mouton, méta-analyse.*

Introduction

The control of animal performance, health and product quality requires an improved understanding of the regulation of nutrient utilisation, especially the partition between tissues and organs. When considering the exchange of nutrients, the liver plays a major role in regulating the metabolism of circulating nutrients and of their subsequent delivery to peripheral tissues. Fluxes of nutrients through the liver depend largely on the respective contributions of the portal blood draining the digestive tract, spleen, pancreas and mesenteric fat, and that of the hepatic arterial blood. Blood nutrient concentrations vary greatly between these two vessels. In the portal vein, concentrations result mainly from the net absorption of nutrients following digestion of feeds in the gastro-intestinal tract. In the arterial blood, concentrations result from the balance between net nutrient absorption, utilisation and mobilisation from tissues.

When calculating the net nutrient fluxes across the liver (Katz and Bergman, 1969a), blood flow in the portal vein and in the hepatic artery have an important quantitative impact. Hepatic arterial blood flow is difficult to measure and most authors use the para-amino-hippuric acid (PAH) dilution method to calculate flow from the difference between the hepatic venous and portal blood flows. Portal and hepatic venous blood flow measurements are associated with large error terms (Isserty *et al*., 1998), leading to an even higher uncertainty for the hepatic arterial blood flow. Ultrasonic flowmetry enables more precise portal blood flow measurements but hepatic arterial blood flow cannot be measured using this technique because of the anatomic characteristics of the hepatic arteries, and associated

surgical difficulties. In this case, hepatic arterial blood flow has to be estimated. Consequently, determining the variation in the contribution of hepatic arterial to total hepatic blood flow, associated with varying dietary conditions, is a key objective in in vivo hepatic metabolism studies.

The statistical meta-analytical approach enables all published data to be combined and analysed to draw quantitative conclusions which cannot be obtained from experimental studies or bibliographic reviews (Sauvant *et al*., 2005). The objectives were to carry out a quantitative review of literature, based on meta-analyses, on the regulation of the hepatic blood flows affected by diets fed to sheep. The influence of dry matter intake (DMI) and of metabolisable energy intake (MEI) were evaluated in relation to total hepatic blood flow, and on the respective contributions of the portal venous and hepatic arterial blood flow to total hepatic blood flow.

Materials and methods

The present study was based on a datafile that included 60 publications on hepatic fluxes in sheep, dating from 1965 to 2003. Only publications which reported data on all afferent and efferent hepatic blood flows were considered and included data from fasting animals. Blood flows, DMI and MEI were expressed on a body weight basis (per kg BW) in order to utilise data from animals of different body weights (Vernet *et al*., 2005).

The meta-analysis required a separation of both within-study and between-study variations as detailed by Sauvant *et al.* (2005) and Vernet *et al*. (2005). Briefly, the within-study variations are due to the influence of independent variables of interest (i.e. of the experimental treatments) with all other conditions being identical. The first step of the meta-analysis involved selection and the coding of treatments which showed changes in the independent variable of interest. In the present study, separate selections were based on treatments that included changes either in DMI, MEI or in the metabolisable energy content of the diet (ME/DM). Groups of treatments were defined, and care was taken to ensure that the dependent variables were not biased by other factors, such as the nature of the diet and the physiological state of the animal. A fourth selection enabled the changes in hepatic arterial blood flow to be evaluated in relation to changes in portal blood flow. All these selections were based on the scientific objectives of the studies using the published standard deviations of the dependent variables (DMI, MEI, ME/DM, portal blood flow).

A covariance model, $Y = \alpha + \alpha_1 + \beta X$, was applied to the selected data to test linear effects. In this model, α (intercept) and β (slope) were coefficients common to all groups of treatments, and α_i corresponded to the effect of the group of treatments i. Because of the presence of only 2 treatments in all the selected groups of treatments, the β_i term (slope of individual groups of treatments) could not be included in the model. Analysis of the model residuals was carried out by checking the distribution, numerical value, contribution to the residual variance, leverage as well as the Cook's distances of standardized residuals (St-Pierre, 2001; Sauvant *et al*., 2005) using Minitab software.

Results and discussion

Changes in hepatic blood flows with DMI and MEI in fed sheep

Effect of DMI and MEI were initially analysed for fed animals, using 7 groups of treatments from 6 publications (Burrin *et al*., 1991, Freetly *et al*., 1995; Goetsch *et al*., 1994; Goetsch *et al*., 1997; Ortigues *et al*., 1994; Patil *et al*., 1995) Within treatment groups, diet composition was held constant so that effects were identical for DMI and MEI. Data were used from both adult and growing sheep, fed at 178 (SD=64) kJ MEI/(d.kg BW); [ranging from 77 to 304 kJ MEI/(d.kg BW) or from 0.5 to 2 fold maintenance]. Forage based or mixed diets were fed with an average ME of 9.6 (SD=1.20) MJ/kg DM (ranging from 8 to 12 MJ ME/kg DM). In all cases, blood flows were measured by PAH dilution, and generally PAH was chemically analysed using an automated method including a dialysis step.

The increase in portal venous, hepatic arterial and hepatic venous blood flows with increasing DMI and MEI (Table 1; Figs 1a, 1b), is well known (Webster *et al*., 1975). Meta-analysis has provided a more robust quantification of blood flows (Table 1) than those from individual publications When DMI

increased by 1 g/(d.kg BW), portal venous, hepatic arterial and hepatic venous blood flows increased by 61, 20 and 81 ml/(h.kg BW) respectively. When MEI increased by 1 kJ/(d.kg BW), blood flows increased by 5.8, 2.0 and 7.8 ml/(h.kg BW). The calculated increase in portal blood flow with DMI was similar to that reported by Vernet *et al*. (2005).

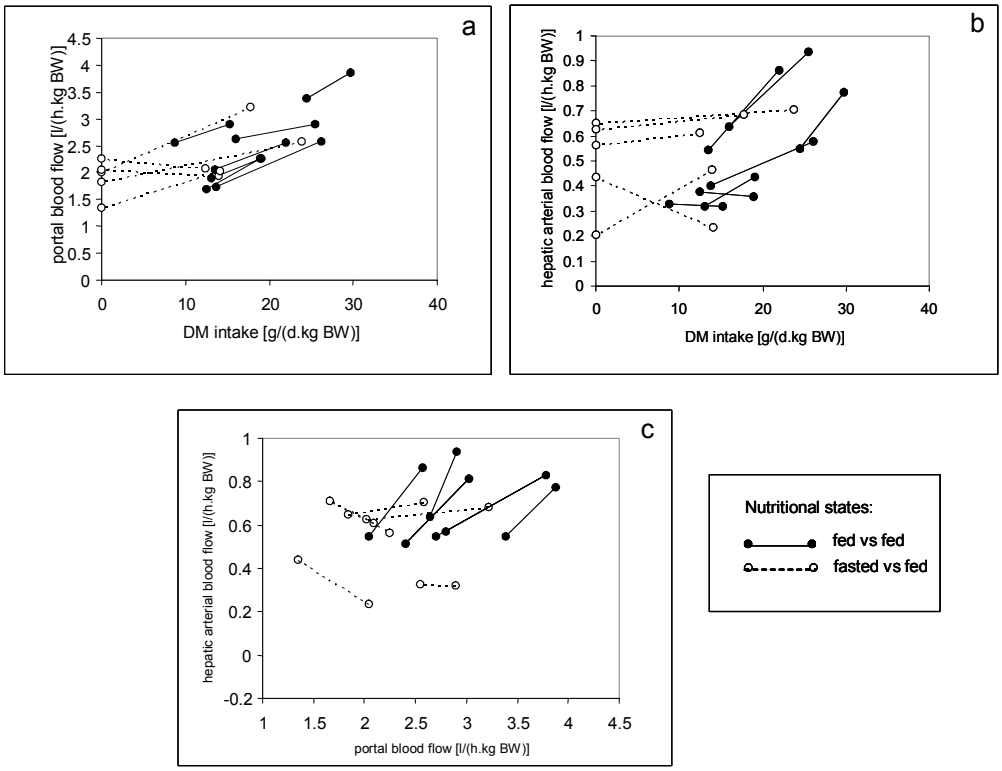

Fig.1 Variations in portal (a) and hepatic arterial (b) blood flow with dry matter (DM) intake and relationships between hepatic arterial and portal blood flow (c) within groups of treatments. Data are from sheep fed either two levels of intakes (fed *vs* fed) or fasting and fed. BW: body weight; DM: dry matter.

Changes in hepatic blood flows with DMI and MEI in sheep that were either fasted or fed

Evaluation of fasting was made using data from adult sheep, using 5 groups of treatments from 4 publications (Bergman *et al*., 1970, Bergman *et al*., 1971, Heitmann *et al*., 1986, Katz and Bergman, 1969b). Animals were either fasted for at least one day or fed [on average 133 (SD=33) kJ MEI/(d.kg BW), range from 103 to 187 kJ ME/(d.kg BW), or 0.9 to 1.5 maintenance]. Forage diets were fed with a ME content averaging 8.2 (SD=0.3, range from 7.9 to 8.5) MJ ME/kg DM. Five groups of treatments were used. In all cases, blood flows were measured by PAH dilution and the chemical determination method of PAH included a deacetylation step (heating) with acid deproteinisation. Changes in blood flows differed from those noted in fed animals (Table 1; Figs 1a and 1b). Hepatic venous blood flow increased with feeding, but to a lesser extent than in fed sheep. A similar trend ($P<0.10$) was noted for the portal blood flow but the hepatic arterial blood flow was not significantly modified by feeding. The relationship between portal blood flow and feed intake below maintenance was lower than that above maintenance, supporting the curvilinear response derived by Webster *et al.* (1975) in sheep fed from 0 to 310 kJ/(d.kg BW). It is unlikely that the differences in slopes between the fed and the fasted *vs* fed states originate from differences in PAH methodology (Isserty *et al*., 1998).

Table 1 Changes in blood flow [β; ml/(h.kg BW)] following changes in dry matter intake [DMI, g/(d.kg BW)] and metabolisable energy intake [MEI, kJ/(d.kg BW)] in sheep that were either fed at different levels of intake or fasted

Independent variable	Blood flow	Nutritional status	N	Slope			RSE	r^2
				β	SD	P<		
DMI	Portal venous	fed *vs* fed	7	61.0	7.9	0.001	120	0.96
		fasted *vs* fed	5	31.5	13.9	0.09	12	0.73
	Hepatic venous	fed *vs* fed	7	81.5	8.2	0.001	124	0.97
		fasted *vs* fed	5	34.1	12.1	0.05	11	0.85
	Hepatic arterial	fed *vs* fed	7	20.4	5.9	0.01	89	0.81
		fasted *vs* fed	5	2.6	4.3	0.57	4	0.81
	Hepatic a/v	fed *vs* fed	7	0.0013	0.0016	0.44	0.0239	0.87
		fasted *vs* fed	5	-0.0017	0.0024	0.52	0.0640	0.47
MEI	Portal venous	fed *vs* fed	7	5.7	0.9	0.001	148	0.94
		fasted *vs* fed	5	3.8	1.8	0.10	379	0.40
	Hepatic venous	fed *vs* fed	7	7.8	0.9	0.0001	149	0.96
		fasted *vs* fed	5	4.2	1.5	0.05	333	0.68
	Hepatic arterial	fed *vs* fed	7	2.0	0.5	0.01	84	0.84
		fasted *vs* fed	5	0.3	0.5	0.57	114	0.59
	Hepatic a/v	fed *vs* fed	7	0.0001	0.0002	0.37	0.0235	0.72
		fasted *vs* fed	5	-0.0002	0.0003	0.53	0.0640	0.54

N, number of groups of treatments; hepatic a/v is the ratio of hepatic arterial / venous flow rates.

Contribution of hepatic arterial to total hepatic blood flow in sheep

In sheep fed about maintenance, the contribution of the hepatic artery to total hepatic blood flow averaged 0.183 (SE = 0.048) ranging between 0.104 and 0.227. These values are obtained using the PAH dilution methodology and are not measured but calculated by difference. The uncertainty of the calculated flows is ± 80% (Isserty *et al*., 1998). In sheep, much lower contributions (2 to 6%) were measured by Barnes *et al.* (1986) using microspheres and calculated by Lobley *et al*. (1995) with the PAH dilution method using an analytical method based on gravimetric manipulations and deacetylation of PAH, and a highly representative blood sampling procedure.

Despite the fact that questions still remain on the exact contribution of the hepatic artery to total hepatic blood flow in sheep, the present study pinpoints the absence of significant changes in the contribution of the hepatic artery to total hepatic blood flow hepatic arterial flow with DMI or MEI (Table 1). This finding was intriguing because the hepatic artery is apparently controlled in a manner that subserves the homeostatic needs of the entire body (Lautt, 1983).

The relationship between hepatic arterial and portal blood flow was studied with treatments that presented a sufficiently wide variation on the portal blood flow. In fed animals, hepatic arterial blood flow increased when portal blood flows increased, whereas no significant changes in hepatic arterial blood flow were noted between fasted *vs* fed sheep despite changes in portal blood flow (Fig. 1c). Present results suggest the contribution of the hepatic artery could decrease from 0.21 to 0.18 of portal flow and subsequently return to 0.20 when intakes increase from 0 to 1 and then to 2-fold maintenance. These quantitative changes remain however low and non significant.

Changes in hepatic blood flows with the metabolisable energy content of the diet

An observation from the relationships in Table 1 is that the residual standard errors of the estimates were generally lower when DMI was used as the independent variable, compared to MEI. This suggests that dietary bulk could have a more important effect than the dietary ME/DM content.

Han *et al*. (2002) also found the increase in portal blood flow with increasing MEI from 50 to 100 kJ /(d.kg BW) was mainly linearly related to bulk. An attempt was made to test the influence of the ME content of the diet, at similar DMI. However, no clear effect could be demonstrated, probably because there was insufficient range in the data available for analysis.

Conclusions

The magnitude of the response of the portal venous and hepatic arterial blood flows with intake (DMI, EMI) differed between fasted *vs* fed and fed *vs* fed animals. However, no significant changes could be detected on the contribution of the hepatic artery to the total hepatic blood flow.

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