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Dietary macronutrients and the aging liver sinusoidal endothelial cell

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Fenestrations are pores within the liver sinusoidal endothelial cells (LSECs) that line the sinusoids of the highly vascularized liver. Fenestrations facilitate the transfer of substrates between blood and hepatocytes. With pseudocapillarization of the hepatic sinusoid in old age, there is a loss of fenestrations. LSECs are uniquely exposed to gut-derived dietary and microbial substrates delivered by the portal circulation to the liver. Here we studied the effect of 25 diets varying in content of macronutrients and energy on LSEC fenestrations using the Geometric Framework method in a large cohort of mice aged 15 mo. Macronutrient distribution rather than total food or energy intake was associated with changes in fenestrations. Porosity and frequency were inversely associated with dietary fat intake, while fenestration diameter was inversely associated with protein or carbohydrate intake. Fenestrations were also linked to diet-induced changes in gut microbiome, with increased fenestrations associated with higher abundance of Firmicutes and reduced abundance of Bacteroidetes. Diet-induced changes in levels of several fatty acids (C16:0, C19:0, and C20:4) were also significantly inversely associated with fenestrations, suggesting a link between dietary fat and modulation of lipid rafts in the LSECs. Diet influences fenestrations and these data reflect both the key role of the LSECs in clearing gut-derived molecules from the vascular circulation and the impact these molecules have on LSEC morphology.

aging; fenestrations; microbiome

NEW & NOTEWORTHY

We demonstrate a link among diet, the gut microbiome, and fenestrations of the liver sinusoidal endothelium. Fenestrations are reorganized in response to diet, potentially in conjunction with the composition and activity of the gut microbiome. The effects of diet and microbiome on the fenestrations have significant implications for liver function into old age.

The sinusoids of the liver are a highly differentiated and specialized vascular bed. The sinusoidal vessels are predominantly perfused with venous blood draining directly from the splanchnic circulation and because of this the blood contains numerous gut-derived molecules. Lining these vessels are the liver sinusoidal endothelial cells (LSECs); these cells have key physiological roles in endocytosis, immune function, and the rapid transfer of substrates between blood and hepatocytes via fenestrations (12, 36, 37). LSECs are ~100-nm thick, perforated with numerous transcellular pores, called fenestrations, and are not associated with basement membrane. With aging, there are significant ultrastructural changes in the LSEC that have been termed pseudocapillarization (20, 23). These include a marked reduction in fenestrations, associated with increased endothelial thickness and altered expression of several endothelial and extracellular matrix proteins including von Willebrand factor and collagen. Pseudocapillarization has been detected in old age in mice, rats, nonhuman primates, and humans (20, 23) and has been documented in premature aging syndromes in mice (9, 13). Fenestrations are dynamic, nondiaphragmed, transcellular pores that allow the free passage of substrates between the sinusoidal blood and hepatocytes (12). Therefore, loss of fenestrations with pseudocapillarization contributes to impaired hepatic clearance of substrates such as lipoproteins and medications in old age (15, 21).

Fenestration number and size are altered by fasting (27), caloric restriction (16), and following exposure to bioactive molecules of gut bacterial origin, which are delivered via the portal vein directly to the liver (5). These properties suggest
that fenestrations are reorganized in response to diet, potentially in conjunction with the effects of diet on the composition and activity of the gut microbiome. Therefore, in this study we determined the outcomes of exposure to different dietary macronutrients and calorie intake on fenestrations in old age. Livers were studied from a large cohort of 15-mo-old mice that had been ad libitum fed 1 of 25 diets varying in the amounts of protein, fat, carbohydrate, and energy density to study the relationship among energy intake, macronutrients, aging, and lifespan (22, 34, 35). In addition to the direct role of individual macronutrients on fenestrations, we were able to explore the effect of diet-induced changes in populations of gut-derived bacteria and circulating metabolites on the structural integrity of the LSEC as potential mechanisms linking diet and fenestrations.

METHODS

Animals. The mice and dietary interventions have been described previously (22, 34, 35). Briefly, C57BL/6 male and female mice (n = 858) were ad libitum fed 1 of 25 diets varying in protein, carbohydrate, and fat content with total energy altered by the addition of indigestible cellulose. All protocols were approved by the Sydney Local Health District Animal Welfare Committee (Protocol No. 2009/003).

Tissue and blood collection. At 15 mo of age, one-third of the animals were euthanized under ketamine and xylazine anesthesia for tissue collection. Just before euthanasia body composition was determined using a GE PIXImus2 Series Densitometer (34). Liver tissue was harvested for scanning electron microscopy and analyzed as previously described (8). Endothelial porosity is the percentage of the endothelial surface perforated by fenestrations and is calculated from their diameter and frequency. Circulating amino acids were analyzed by the Australian Proteome Analysis Facility, and free fatty acids were analyzed by Metabolomics Australia while insulin and leptin were measured by ELISA (ALPCO Diagnostics).

Gut microbiome. The cecum contents were collected, metagenomic DNA was recovered, and the microbial community was sampled by 454 sequencing of the 3’-end of the 16S ribosomal RNA (907–1492) using primers specific for the domain bacteria (18). Sequence reads were assigned to operational taxonomic units at 97% identity and then classified using both QIIME and Mothur (4, 31).

Statistics. The effects of macronutrient intake on fenestrations were analysed using the Geometric Framework approach, with response variables fitted as response surfaces onto macronutrient intake (protein, carbohydrate, and fat) arrays, using thin-plate spline procedures in R (2) accompanied by generalized additive modeling to test the main and interactive effects of the three macronutrients. These methods are described elsewhere (22, 34, 35).

To explore the relationship among fenestrations, dietary macronutrients and the gut microbiome correlations were performed using the Spearman’s test in SigmaPlot (SPSS Version 12.5). To further explore these relationships we then tested whether abundance of circulating metabolites (fatty acids and amino acids) and bacterial higher taxa correlated with fenestration morphology using an information theoretic, model averaging approach with linear models (LMs) (3). We assessed whether dietary correlates affected three aspects of fenestrations: 1) percent porosity [converted to a proportion and logit transformed to normalize (40)], 2) diameter of the fenestration, and 3) fenestration frequency [+0.5 and log transformed to normalize (42)]. LMs were fitted using the “lm” function in the R base package and model averaging was performed using the package MuMIn (1).

RESULTS

Geometric framework analysis of the relationship between macronutrients and LSEC fenestrations. Response surfaces showing the relationship among macronutrients, dietary en-

![Fig. 1](http://api.ajpheart.physiology.org/images/1065/H1065MACRONUTRIENTS, MICROBIOME, AND FENESTRATIONS_H1065.png)

Fig. 1. Geometric Framework analysis showing the relationship between macronutrients and fenestration porosity (A) and diameter (B). In each surface, blue represents the lowest value while red represents the highest value. Each graph represents a slice through the median value of the third macronutrient (value provided in parenthesis below the x-axis label). Three graphs are provided demonstrating the interactions between protein and carbohydrate, protein and fat, and carbohydrate and fat. The regions with the highest fenestration diameter porosity or diameter are encircled in red, while those with the lowest are encircled in blue. Fat had a significant effect on porosity (P = 0.016) while protein and carbohydrate had significant effects on diameter (P = 0.028 and P = 0.006, respectively).
Fig. 1. Diabetes and fenestration porosity and diameter are shown in Table 1 (n = 129 mice, at least 3 mice per diet treatment, male and female mice combined as individual sex analyses showed no difference, data not shown) and representative scanning electron micrographs are shown in Fig. 2. Fenestration porosity was influenced by dietary fat intake (P = 0.016; Table 1), with low to intermediate fat intakes (~20 kJ·mouse$^{-1}·$day$^{-1}$) associated with highest porosity, and porosity falling both as fat intake increased or decreased to very low levels indicating a nonlinear (quadratic) effect. There was no statistically significant impact of the intake of energy, protein, or carbohydrate on porosity.

The response of fenestration frequency was similar to that of porosity, being associated only with fat intake (P = 0.001). On the other hand, fenestration frequency was inversely associated with protein and carbohydrate intakes (P = 0.028 and P = 0.006, respectively). Low carbohydrate or low protein intake were both associated with increased fenestration diameter. However, there were no interactions between protein and carbohydrate, and their impact on diameter was not sufficient to translate into a change in total porosity. There were no correlations between fenestrations (porosity, frequency, or diameter) with body weight (P = 0.7, 0.7, and 0.4, respectively) or body fat determined by DEXA measured by the PIXImus2 Densitometer (P = 0.7, 0.7, and 0.4, respectively).

Relationship between fenestrations and gut microbiome. There were 78 mice where a complete dataset was available for both electron microscopy of the LSEC and gut microbiome analysis. In this cohort of samples the most abundant taxa were the Firmicutes and Bacteroidetes phyla, followed by Clostridia, Bacillae, Erysipelotrichia, Deferrribacteres, Verrucomicrobia, Lachnospiraceae, Clostridiaceae, Ruminococcaceae, Eubacteriaceae, Rikenellaceae, and Bacteroidaceae. There were significant positive relationships between fenestration porosity and diameter with the abundance of the Firmicutes phylum (Fig. 3; P = 0.046 and P = 0.0057, respectively). There was a significant negative relationship between fenestration diameter and the abundance of the Bacteroidetes phylum (P = 0.045) and a nonsignificant negative trend with fenestration porosity and Bacteroidetes (Fig. 3; P = 0.087).

Table 1. GAMs for Fig. 1

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<th>Porosity (Fig. 1A)</th>
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<th>Degrees of Freedom</th>
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<td>0.000</td>
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<td>0.1218</td>
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<td>Fat eaten</td>
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<td>8</td>
<td>0.698</td>
<td>0.1076</td>
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<tr>
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<tr>
<td>Carbohydrate, fat eaten</td>
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<table>
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<td>0.000</td>
<td>0.02760*</td>
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<td>8</td>
<td>0.000</td>
<td>0.00635**</td>
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<td>Fat eaten</td>
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<td>Protein, fat eaten</td>
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Fig. 1A: R sq. (adj.) = 0.0942. Deviance explained = 11.7%. REML = 234.77. Scale est. = 2.1008; n = 129. Fig 1B: R sq.(adj.) = 0.052. Deviance explained = 6.42%. REML = 272.02. Scale est. = 3.8373; n = 129. GAMs, generalized additive modeling; edf, estimated degrees of freedom; REM, restricted maximal likelihood. *P < 0.05; **P < 0.01.
Model averaging of lower taxonomic orders indicated that no bacterial families were particularly good predictors of fenestration diameter or porosity (all families had a relative importance <0.6), and for both responses the top model sets included the null models (data not shown, available on request). However, in concordance with the relationships suggested above, model averaging suggested that increasing *Firmicutes* abundance (a member of the *Bacteroidetes* phylum) was associated with decreasing frequency of fenestrations [LM Est. (lower to higher confidence interval (LCI to UCI)] = −0.603 (−0.954 to −0.252) and increasing abundance of *Lachnospiraceae* (a member of the *Firmicutes* phylum) was associated with an increase in fenestrations [LM Est. (LCI to UCI) = 0.422 (0.063 to 0.781)].

Relationship between fenestrations and circulating metabolites and other substrates influenced by diet. Correlative analysis of individual free fatty acids found negative relationships between C16:0 (palmitic acid) and C20:4 (arachidonic acid) with fenestration porosity (P = 0.027 and P = 0.037, respectively, n = 95 mice), while C19:0 (nonadecanoic acid) had negative associations with fenestration diameter (P = 0.020; Fig. 4, B–D), as well as frequency (P = 0.048, data not shown). However, model averaging of free fatty acid groups showed that despite the strong influence of dietary fat intake had on fenestration morphology, circulating levels of fatty acids were not good predictors of fenestration responses: in all cases the relative importance of predictors was <0.45, and for all three responses the top model set contained the null model. In addition, there were no associations between fenestrations and other measures that reflect metabolic health, including blood glucose, insulin, triglycerides, cholesterol, or leptin, although there was a nonsignificant trend towards a negative relationship between fenestration diameter and fasting insulin.

There were no significant relationships among fenestration porosity, diameter, or frequency with circulating levels of total amino acids, total branched chain amino acids, or any of the individual amino acids except phenylalanine, which had a negative relationship with porosity (P = 0.037, n = 94 mice; Fig. 4A), and aspartic acid, which had a negative relationship with diameter (P = 0.047). Model averaging of more complex models also indicated that the concentration of circulating amino acids was not a good predictor of fenestration diameter or frequency; in both cases the top model sets contained the null models. The best predictor was abundance of hydroxyl and sulfur selenium amino acids, which had a relative importance of 0.832 for the fenestration diameter response, and was estimated to have a positive effect but with very poor precision [LM Est. (LCI to UCI) = 11.779 (−1.075 to 24.633)]. For fenestration porosity, abundance of aliphatic amino acids had a relative importance of 1, appearing in all models in the top model set. Model averaged estimates indicate that increases in aliphatic amino acids were associated with decreases in the endothelial porosity [LM Est. (LCI to UCI) = −0.431 (−0.799 to 0.063)].

**DISCUSSION**

In previous studies, fenestrations have been reported to be influenced by reduced intake of food and dietary energy. In one study, we showed that a 48-h period of fasting in rats was associated with increased fenestration diameter of ~10% (27). In another study, we found that caloric restriction over a lifetime in rats was associated with increased fenestration
frequency and porosity of ~60% in old age (16). These studies indicate that fenestrations are dynamic structures that are influenced by dietary manipulation. However, studies where only one nutritional dimension, energy, is manipulated cannot determine whether the outcome is a result of a reduction in total energy or one of the individual macronutrient components of the diet (32). One of the key advantages of using the Geometric Framework is that the different components of the diet, energy, protein, carbohydrates, and fat, and their interactions can be evaluated across a nutritional landscape (33). The results of this study have revealed that the main dietary component that influences fenestration porosity is fat, such that higher fat intakes are associated with reduced fenestration frequency and overall porosity. A low fat intake of ~20 kJ·mouse⁻¹·day⁻¹ was associated with maximum porosity; however, below this level porosity decreased again slightly. According to the phenotype response surfaces, porosity varied between ~2.8 and 4.4% depending on the dietary fat intake. Fat intake had its main impact on fenestration frequency while protein and carbohydrate intakes influenced fenestration diameter, although this was not sufficient to alter total porosity.

A number of nutritional interventions have been found to influence aging and lifespan with the most widely studied being caloric restriction. We have previously shown that caloric restriction is associated with increased fenestrations in old age (16). The results in our current study suggest that this might be secondary to a reduction in each of the macronutrients acting via different mechanisms: the reduction in fat intake leading to increased fenestration diameter, the reduction in protein and carbohydrate intake leading to increased fenestration frequency. On the other hand, our studies in insects (24) and mice (34) have indicated that low-protein, high-carbohydrate diets are linked with longer lifespan and improved late life health. We did not find any direct beneficial impact of low-protein, high-carbohydrate diets on fenestrations, perhaps as a consequence of the opposing effects of low protein and high carbohydrate on fenestration diameter.

Having established that macronutrients influence fenestrations we then sought to elucidate possible mechanisms that could link diet with LSEC ultrastructure. We performed analysis of gut microbiome and circulating fatty acids and amino acids. Analysis of the gut microbiome data showed a positive relationship between fenestrations and diet-induced changes in the Firmicutes phylum and a negative relationship and/or trend with the Bacteroidetes phylum. Firmicutes and Bacteroidetes make up the most abundant phyla within the gut microbiome. Fundamental differences in the cell wall composition of these two phyla may mean a significant difference in microbe associated molecular patterns (MAMP) exposure leading to different outcomes. Although the abundances of Firmicutes and

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**Fig. 4.** The relationship between phenylalanine (A) and the fatty acids C16:0 (B), C20:4 (C), and C19:0 (D). There were significant correlations between porosity and circulating phenylalanine ($P = 0.037, r = 0.215$), C16:0 ($P = 0.027, r = -0.227$), and C20:4 ($P = 0.037, r = -0.216$) and between fenestration diameter and C19:0 ($P = 0.020, r = -0.238$).
Bacteroidetes have been linked to various health states, these phyla include a broad diversity of different taxa of bacteria, thus analysis limited to Firmicutes and Bacteroidetes can only be considered to be a blunt interpretation of gut microbiota (14, 17). The existence of autocorrelation, whatever its basis, may mean there will be alignment among MAMP profiles of bacteria, the frequency and size of fenestrations, and the extent of transfer of substances across the endothelium, and this feedback mechanism between these factors needs further elucidation. Nonetheless, it is interesting that the abundance of Firmicutes declines with age while Bacteroidetes increases (17, 25). Aging is associated with a reduction in fenestrations, which is a key part of age-related pseudocapillarization of the hepatic sinusoid (20, 23), which might therefore be mechanistically linked with age-related changes in the relative abundances of Firmicutes and Bacteroidetes. There has also been a growing focus on the role of the gut microbiome in the pathogenesis of hepatic diseases including in particular hepatosteatosis and cirrhosis (41). This is in part because the liver receives the majority of its blood supply from the intestinal portal circulation, and is therefore exposed to a diverse array of microbial toxins and metabolites. Hepatosteatosis has been reported to be associated with reduced microbial toxins and metabolites. Hepatosteatosis has been linked with age-related changes in the relative abundances of Firmicutes and Bacteroidetes. This has also been a growing focus on the role of the gut microbiome in the pathogenesis of hepatic diseases including in particular hepatosteatosis and cirrhosis (41). This is in part because the liver receives the majority of its blood supply from the intestinal portal circulation, and is therefore exposed to a diverse array of microbial toxins and metabolites. Hepatosteatosis has been reported to be associated with reduced Firmicutes and increased Bacteroidetes, while various liver diseases associated with leaky gut promote increased exposure of the liver to bacterial toxins and bacteria (10, 28, 41). In fact, we have previously shown that LSEC defenestration can be caused by direct exposure to two bacterial toxins: lipopolysaccharide endotoxin (10) and pseudomonal pyocyanin (6). Although we did not see a correlation with the most prolific producers of endotoxin, Proteobacteria, in this experiment (data not shown), this may be because the recovery of these particular phyla is outside the resolving capacity of this data. Of further note is the constitutive LSEC expression of TGR5, a receptor targeted towards the bacterially modified bile metabolites. TGR5 regulates the production of vasoactive endothelial nitric oxide synthase and may link the changes we see here between fenestrations, macronutrients and microbial community change (particularly lower Firmicutes) (39).

We then investigated the relationship between circulating substrates that might reflect changes in dietary intake of macronutrients. Our previous studies have demonstrated that fenestrations form in the nonlipid raft segments of the LSEC cell membrane (38). Moreover, interventions that disrupted lipid rafts and the nonraft membranes had significant effects on fenestrations and porosity. We concluded that one of the factors regulating fenestrations was lipid rafts (7, 38). Lipid rafts are potentially influenced by diet, in particular dietary fatty acids (11). The lipid rafts contain a high proportion of saturated fatty acids while long chain polyunsaturated fatty acids increase the clustering of proteins within lipid rafts (19). A number of different fatty acids, including arachidonic acid (C20:4), partition rapidly into cell membranes and perturb lipid rafts (19). Furthermore, it has been demonstrated that metabolites of arachidonic acid contribute to LSEC dysfunction in the setting of portal hypertension (30). Therefore, it is of note that circulating levels of the saturated fatty acids, C16:0, C19:0, and the polyunsaturated fatty acid C20:4 were associated with fenestrations. However, more complex models could not find substantial correlations between fatty acid groups and fenestrations.

In our Geometric Framework study of the effects of macronutrients on aging, we found that branched chain amino acids appeared to mediate some of the benefits of a low-protein, high-carbohydrate diet on age-related health and lifespan (34). Here we did not find any association between branched chain amino acids and fenestrations. Examination of the other amino acids revealed an inverse association between porosity and phenylalanine concentrations. Although this could be a chance finding, it is of note that an elevated level of phenylalanine is a risk factor for hypertriglyceridemia (26), while defenestration is a mechanism for hyperlipidemia through impaired hepatic uptake of chylomicron remnants (15).

In conclusion, macronutrient intake had complex effects on LSEC fenestrations. Overall, reduced intake of macronutrients was associated with increased measures of fenestration frequency and/or diameter, with fat having the dominant influence on porosity mediated by its effect on the frequency of fenestrations. There was an association among diet-induced changes in microbiome (Firmicutes, Bacteroidetes), diet-induced changes in free fatty acids, and fenestrations, which could provide mechanisms linking diet to changes in LSEC ultrastructure.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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