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Of Microbes and Meals: The Health Consequences of Dietary Endotoxemia

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Abstract

The human intestinal tract is comprised of a rich and complex microbial ecosystem. This intestinal microbota provides a large reservoir of potentially toxic molecules, including bacterial endotoxin (i.e., lipopolysaccharide). This potent inflammatory molecule is detectable in the circulation of healthy individuals and levels transiently increase following ingestion of energy rich meals. Chronic exposure to circulating endotoxin has been associated with obesity, diabetes, and cardiovascular disease. Western-style meals augment LPS translocation and by this mechanism may contribute to the pathogenesis of these diseases. By contrast, the gut and other organs have evolved mechanisms to detoxify endotoxin and to neutralize the potentially inflammatory qualities of circulating endotoxin. Of specific interest to clinicians is evidence that acute postprandial elevation of circulating endotoxin is dependent on meal composition. In this review we present an overview of the biochemical and cellular mechanisms that lead to endotoxemia, with emphasis on the interplay between microbial and nutritional determinants of this condition. The link between endotoxemia, diet, and changes in the intestinal microbiota raise the possibility that dietary interventions can, at least in part, ameliorate the detrimental outcomes of endotoxemia.

Keywords

gut; microbiota; microbiome; inflammation; postprandial; endotoxin; endotoxemia; lipopolysaccharide; obesity; diabetes

Introduction

The gastrointestinal tracts of humans and other mammals are complex bioreactors that have evolved to extract nutrients from diverse natural products. Critical to the functions of these

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systems are dynamic communities of microorganisms that likely have co-evolved with their hosts to provide myriad beneficial services, including nutrient provision.[1] The high-carbohydrate diets ingested by omnivores and herbivores typically contain plant polysaccharides that cannot be directly hydrolyzed by the mammalian gut. Instead, the intestinal microbiota, which in adults is dominated by diverse members of the bacterial phyla Firmicutes (e.g., clostridia) and Bacteroidetes,[2–4] encodes a variety of hydrolytic enzymes that can convert otherwise indigestible polysaccharides into relatively simple compounds such as short-chain fatty acids (SCFAs), which are more readily absorbed by the mammalian intestines.[1] In this way, the microbiota collectively provides genomic coding capacity -- the "microbiome"[5,6] -- that supplements the function of the host genome. That mammalian breast-milk is composed of many types of oligosaccharide that both direct the early development of the intestinal microbiota and are fermented by this microbiota into compounds that nourish the developing infant is testament to the deeply interlinked relationships between host and microbiota.[7,8]

The intimate association of numerically rich and diverse microbial communities with the human host potentially comes at a price. Commensal microorganisms are, in many instances, separated from the interior of the body by a single layer of epithelial cells, which in the case of the distal gut must form a barrier to entry of as many as 10^{12} microbial cells per gram of luminal content.[9] To prevent potentially lethal microbial infections, the immune system is tuned to detect and respond to microbes that breach the epithelium. A variety of chemical moieties that are conserved across broad ranges of microbes – termed microbe-associated molecular patterns (MAMPs) – trigger signaling cascades in diverse host cells that result in recruitment and activation of innate and adaptive immune effector cells to sites of infection. Once the threat of infection is mitigated, the immune system must be down-regulated in order to prevent prolonged, destructive inflammation. For example, an inability to quell localized inflammatory responses to the intestinal microbiota is a hallmark of the inflammatory bowel diseases.[10]

Despite diligent immune surveillance, small amounts of gut-derived bacterial MAMPs, such as endotoxin (i.e., lipopolysaccharide, LPS), enter the circulation of healthy mammals,[11] possibly as the result of particular diets. Systemic exposure to MAMPs may incite low-level, chronic inflammation even in the absence of viable microbial cells in the bloodstream. The deleterious effects of such persistent exposure to inflammatory inducers have been proposed to be causal factors in the development of metabolic syndrome.[12] The purpose of this review is to provide clinicians and healthcare professionals with an overview of the biochemical and cellular mechanisms that lead to endotoxemia, with emphasis on the interplay between microbial and nutritional determinants of this condition.

Postprandial Endotoxemia

Recent human clinical trials[13–17] demonstrate a transient increase of circulating LPS following consumption of an energy rich meal and suggest a mechanistic link between diet, postprandial inflammation, and disease. Great interest has surrounded these trials because circulating LPS is associated with inflammatory mediators,[18] and obesity,[18,19] diabetes,[20,21] steatohepatitis,[22] renal,[19,23] and cardiovascular disease.[24] LPS is the primary structural

component of the outer membrane of Gram-negative bacteria. It is composed of carbohydrate containing domains and the highly-immunogenic lipid-A domain. Extensive species-specific variation exists between the carbohydrate containing domains whereas the lipid-A domain is highly conserved. This conserved domain provides MAMPs for host immune recognition by the LPS receptor, Toll-like receptor 4 (TLR4).[25] Several events must take place before LPS can bind and signal through TLR4. First, LPS must bind the secreted LPS-binding protein (LBP), an acute phase protein synthesized in the liver and lung.[26,27] The LBP-LPS complex is then capable of binding CD14, which exists in soluble and membrane bound forms. Finally, the LPS/LBP/CD14 complex is capable of signaling through TLR4, leading to downstream inflammatory responses.[28]

In 2007, Erridge, et al[17] published results of a feeding trial in humans that demonstrated postprandial endotoxemia following ingestion of a single high fat meal. Twelve healthy men were fed a 900 kcal meal (3 slices of toast with 50 grams of butter). Median plasma LPS concentration increased by 50% (8.2 pg/mL baseline; 12.3 pg/mL postprandial). Elevated plasma LPS also was observed following the feeding of healthy subjects egg and sausage muffin sandwiches and hash browns in a meal that contained similar energy and fat content.[16] More recently, Laugerette, et al reported a similar outcome following ingestion of a moderate fat meal (882 kcal, 33% fat).[13] Only one study has attempted to identify specific macronutrients responsible for postprandial endotoxemia. In this study,[15] healthy participants were given only 300 kcal of either: glucose drink (100% carbohydrate), orange juice (92% carbohydrate), or cream (100% fat). Only the cream caused elevation of plasma LPS (41% increase). In a cross sectional study, Amar, et al[29] measured circulating LPS in 201 French adults randomly selected from polling lists. A dietitian-reviewed 3-day food record enabled correlation of circulating LPS with macronutrient intake. Plasma LPS concentration was independently associated with total energy intake, but not fat intake. Taken together, current evidence indicates that endotoxemia can result from a variety of diets that range from 300 kcal of pure cream,[15] to a more typical 882 kcal (33% fat),[13] to the relatively large 1,200 kcal (38% fat).[14] The demonstration that 300 kcal of cream is sufficient to produce endotoxemia raises the important question of whether other dietary lipids, protein, and non-glucose carbohydrates may also induce endotoxemia. As the role of endotoxemia in the pathogenesis of common diseases becomes better established, making these determinations will become increasingly important.

Mechanisms of Translocation

Multiple theories seek to explain how gut-derived LPS navigates into the circulation.[30] One hypothesis proposes that impaired epithelial resistance associated with a high energy intake permits paracellular (between epithelial cell) movement (figure 1). Evidence supporting this model comes from Cani, et al[31] who demonstrated increased intestinal permeability to an inert fluorescent molecule in mice fed a high fat (72% kcal) diet, whereas permeability was not detected in mice fed a standard diet. Furthermore, these animals had reduced expression of the tight junction proteins, ZO-1 and occludin. Barrier integrity was also studied by Brun, et al[32] who utilized mice deficient in leptin (*ob/ob* mice) and the leptin receptor (*db/db* mice). Loss of leptin, a hormone that suppresses appetite and energy intake caused both hyperphagia and obesity in these animals. In this study, less electrical resistance and greater

permeability to horseradish peroxidase was observed in small intestine tissue from *ob/ob* and *db/db* mice compared with wild type mice. Immunofluorescence staining demonstrated redistribution of tight junction proteins ZO-1 and occludin away from the cellular border. Importantly, these mice exhibited elevated LPS in the portal circulation even when consuming a standard diet.

Another hypothesis that could explain impaired barrier integrity following high energy intake comes from work by Kvietys, et al[33] who reported epithelial injury in response to normal digestion in the small intestine. They perfused physiologic quantities of glucose, hydrolyzed casein, and bile emulsified oleic acid into the jejunum of anesthetized rats. In contrast to the benign effects of the carbohydrate and protein treatment, the oleic acid emulsion induced a transient epithelial injury at the villous tips and increased intestinal permeability (similar results were also found in pigs[34,35] and dogs).[36]

Alternatively to paracellular LPS transport, a transcellular pathway (through epithelial cells) is another potential route for LPS entry (figure 1). Cellular uptake of LPS occurs in cultured intestinal epithelial cells.[37] In a mouse model, Ghoshal, et al[30] identified increased LPS in plasma chylomicron remnants following gavage with 200ul of long-chain triolein, a triglyceride of the long-chain oleic acid, which enters the circulation through the lymphatics in chylomicrons. In contrast, gavage with butyrin, a triglyceride of butyric acid, enters directly into portal circulation, but does not raise circulatory LPS levels. In this model system, treatment with an inhibitor of chylomicron formation prevented the increase of LPS in the circulation and mesenteric lymph nodes. An *in vitro* system, utilizing intestinal epithelial monolayers, confirmed these results and in contrast to the previously mentioned effect of oleic acid on tight junctions, no change in permeability to fluorescent dextran was observed. The transcellular model in which lipid digestion and micelle transport facilitate LPS absorption is further strengthened by evidence that LBP increases transport of LPS from micelles to lipoproteins,[38] including chylomicrons,[30,39–41] HDL,[42,43] and LDL.[44] In addition to lipid facilitated LPS transport, nutrient independent uptake might explain baseline fasting levels of LPS in circulation. In support of this idea, Drewe, et al[45] employed *in situ* injection of fluorescently labeled LPS into ligated jejunal loops of fasted rats. They identified LPS absorption into jejunal brush border membrane vesicles. Further studies indicated that this process was disrupted by a metabolic (dinitrophenol) and microtubule inhibitor (colcemid) indicating active LPS uptake. Taken together, these studies implicate multiple, non-exclusive pathways for LPS translocation into the circulation, though transport in micelles may best account for post-prandial endotoxemia.

Microbiota and Endotoxemia

Acute changes in gut bacteria following ingestion of high energy meals could also contribute to endotoxemia by shifting the balance of LPS producing and non-producing microorganisms in the gut. Recent advances in sequencing and genomics have facilitated study of these collective organisms (the microbiota) and their collective genome (the microbiome) at a new level of resolution. An association of endotoxemia with obesity[18] makes it possible that properties unique to the obese microbiota contribute to endotoxemia. Conflicting data support supposed differences in the microbiota when obese are compared to

lean individuals. Although multiple studies have reported greater abundance of Firmicutes and concomitantly reduced abundance of Bacteroidetes in obese subjects,[3,5] others have produced seemingly contradictory results.[46–50] The results of interventional trials raise the possibility that this discrepancy might be explained by the rapid adaptation of the microbiota to ingested nutrients such that the effect of recent energy intake (weight loss vs. maintenance vs. gain) is dominant. For example, no baseline differences in Firmicutes or Bacteroidetes were detected comparing lean and obese humans in a controlled environment while they consumed a weight maintenance diet.[46] However, the composition of the microbiota distinctly changed when subjects were switched between 2,400 and 3,400 kcal diets with Firmicutes and Bacteroidetes positively and negatively associated with energy intake respectively. A similar response in Firmicutes and Bacteroidetes was observed in individuals who lost weight with[48,51] or without[3,52,53] gastric bypass surgery. It is also evident that high fat diets alter the microbiota[31,54] and that this can occur independent of the obese state.[54,55]

The influence of the gut microbiota, the dominant source of LPS among commensal microbiota, on postprandial endotoxemia was demonstrated through antibiotic treatment that reduced the gut bacterial load and caused a decrease of plasma LPS in mice fed a high fat diet. In contrast, plasma LPS did not decrease in control animals that received antibiotics.[31] In animals consuming the high fat diet, antibiotic treatment also restored expression of ZO-1 and ameliorated the adverse effects of diet on intestinal permeability. Interestingly, manipulation of the microbiota with an oligofructose prebiotic dietary supplement normalized plasma LPS. Several mechanisms may underlie the ability of the microbiota to influence endotoxemia. First, the luminal concentration of LPS may be important. The ratio of total enteric LPS (>1 gram)[56] to the large surface area of the gut (>300m^2) suggest that the law of mass action may contribute to LPS translocation. However, animals subjected to high energy diets have decreased bacterial loads per gram of cecal material.[31,54,57] In addition, Gram-negative members of the prominent Bacteroidetes phylum decrease in abundance on such diets,[55,58] whereas Gram-positive clostridiales, a prominent class of the phylum Firmicutes, expand in abundance.[54,55] Despite several recent studies linking energy intake and the microbiota, it is not clear that high energy meals induce endotoxemia by increasing the luminal LPS concentration. Perhaps as important as considering which bacteria proliferate in response to high energy diets is identification of bacterial populations that contract and may thereby transiently stimulate endotoxemia through release of LPS or other factors.

Endotoxemia and Inflammation

Four of the five human feeding trials that documented postprandial endotoxemia also sought evidence of concurrent inflammation. A meal consisting of egg and sausage muffin sandwiches with hash browns (900 kcal, 51 g fat) caused activation of circulating mononuclear and polymorphonuclear cells.[14] The immune response included increased generation of reactive oxygen species (ROS), as well as increased expression of peptidoglycan-sensing TLR2, and the LPS-sensing TLR4.[16] The moderate fat meal (882 kcal, 33 g fat) used to induce endotoxemia by Laugerette, et al[13] increased circulating IL-6 and the TLR4 co-receptor, CD14. These findings are in line with other studies describing acute postprandial elevation of IL-6 (Table 1). Finally, Deopurkar, et al[15] compared 300

kcal of cream, glucose drink, and orange juice. Only the cream caused a rise in plasma LPS and mononuclear cell TLR4, yet the cream and the glucose drink increased several inflammatory markers, including mononuclear cell NF-κB binding activity, TNF-α, and IL-1β, indicating that not all aspects of postprandial inflammation are dependent on endotoxemia. In fact, it remains difficult to attribute postprandial inflammation directly to translocation of gut-derived LPS. Although an acute elevation of circulating IL-6 is typically induced by both high-fat meals and direct LPS infusion in healthy participants (Tables 1, 2), other mediators do not correlate. For example, the effect of a high fat meal on circulating TNF-α and CRP is highly variable and often at odds with the consistent elevation that follows direct LPS infusion (Tables 1, 2). Some evidence indicates that circulating LPS following a meal is less "toxic" than native LPS. For example, Erridge, et al[17] report median postprandial LPS at 12.3 pg/mL and that human plasma supplemented with commercially available LPS to 10 pg/mL induced adhesion molecule expression in human primary aortic endothelial cells and TNF-α in freshly collected human monocytes. Surprisingly, plasma samples from their clinical study were not able to produce these effects despite containing even higher concentrations of LPS. This may reflect a weakness in the predominant method used to quantify LPS (Limulus Amebocyte Lysate assay), which does not differentiate between the "toxic" (diphosphoryl) and "nontoxic" (monophosphoryl) LPS[59] (see later). Moreover, LPS-independent mechanisms may account for postprandial inflammation. For example, free fatty acids alone can induce expression of TNF-α and IL-6 in macrophages, adipocytes, and adipose tissue in a TLR4 dependent pathway.[60] Thus it remains difficult to appraise the contribution of gut-derived LPS to postprandial inflammation in humans. Another area of uncertainty surrounds the phenomenon of LPS tolerance, in which prior exposure to LPS renders an individual less responsive to subsequent challenge[61]. Little is known about induction of LPS tolerance in the context of postprandial endotoxemia, but such a scenario is imaginable.

In contrast to uncertainty surrounding human data, a direct link between postprandial endotoxemia, inflammation, and morbid sequelae was thoroughly demonstrated in animal experiments by Cani, et al.[31,58] In these studies, mice fed a high fat diet (72% fat, 28% protein) consumed twice the energy as controls, exhibited elevated plasma LPS, and acquired features of metabolic disease that could be reproduced by a 4-week infusion of low-dose LPS through osmotic pumps. Both oral antibiotics that prevented endotoxemia and the $CD14^{-/-}$ genotype with defective LPS signaling ameliorated nearly every inflammatory, oxidative, and metabolic derangement in both high-fat-fed and leptin-deficient mice. Work by de La Serre, et al[54] offers insight that might reconcile the apparent conflict between human and animal data. They took advantage of an observation that some Sprague-Dawley rats are susceptible, while others resist, diet induced obesity. Obesity-resistant animals avoided excess energy intake on the high fat diet and maintained expression of intestinal alkaline phosphatase (ALPI), an enzyme that detoxifies LPS (see later). By contrast, obesity-prone rats displayed reduced ALPI activity presumably accounting for the observed increased intestinal permeability and TLR4 activation. Thus, the capacity of the gut to detoxify LPS might account for variation between animal and human data.

LPS Detoxification

It remains unclear how much of post-prandial circulating LPS is available to activate the classical TLR4-dependent inflammatory response. There are, for example, endogenous mechanisms at the various mucosal surfaces to detoxify/inactivate LPS. Standard assays used to measure LPS in serum (e.g. limulus lysate assay) are not able to distinguish LPS which is active or inactive on mammalian cells (see below).

There is much recent interest in intestinal alkaline phosphatase (ALPI), a 70 kDa GPI-anchored protein expressed on the apical (luminal) aspect of intestinal epithelial cell[62], in the detoxification of LPS. In the past, ALPI had been viewed as one of the better epithelial differentiation markers, with little understanding of the true function of this molecule within the mucosa. More recent studies have identified ALPI as a central player in microbial homeostasis.[63–65] Surface expressed ALPI has been shown to retard Gram negative bacterial growth and to potently neutralize LPS through a mechanism involving dephosphorylation of 1,4'-bisphosphorylated glucosamine disaccharide of LPS lipid A (figure 2).[64,65] The resulting monophosphoryl lipid-A is unable to initiate the classical LPS-dependent inflammatory response. ALPI is active beyond the epithelial surface. It was shown to be secreted into the lumen and impart a LPS-dephosphorylating property to the stool.[63] Furthermore, intracellular colocalization with absorbed lipid droplets provide further opportunity for LPS detoxification (figure 2).[66] In a striking demonstration, administration of calf ALPI prevented death of mice injected with a lethal dose of *E. coli*.[67] ALPI appears to affect live bacteria as well. In an animal model, oral administration prevented translocation of live bacteria to the mesenteric lymph nodes following intestinal injury.[63] A role for ALPI in shaping the gut microbiota has been recently identified wherein it maintains an environment favorable to commensal organisms and inhibitory to pathogenic *Salmonella typhimurium*.[68] Relevant for this review, ALPI was recently shown to be highly induced by resolvin E1 (RvE1), an omega-3 fatty acid-derived lipid mediator which promotes the resolution of inflammation.[69] In this study, Cambell et al screened epithelial cells expressing the RvE1 receptor by microarray and revealed a prominent and specific induction of ALPI by RvE1. Surface expressed ALPI was shown to detoxify extracellular LPS and to retard the growth of *E. coli*. Likewise, administration of RvE1 to mice in an in vivo colitis model revealed that decreased disease activity strongly paralleled tissue ALPI levels and that inhibition of ALPI reversed such protection. These data provide a previously unappreciated role for ALPI in omega-3 fatty acid-mediated inflammatory resolution.

LPS sequestration may also prevent an inflammatory response during postprandial endotoxemia. Possible mechanisms include anti-LPS antibodies[70] and LBP mediated uptake by chylomicrons,[30,39–41] LDL,[44] and HDL.[42,43] LBP itself has a dual role; at low concentrations it can facilitate LPS-TLR4 signaling, whereas at high concentrations LBP paradoxically blocks the inflammatory effects of LPS.[71]

Other antimicrobial peptides exist which can inactivate or detoxify LPS. For example, bactericidal/permeability increasing protein (BPI) shares structurally similarity with LBP and is capable of binding and neutralizing LPS. BPI is a 55–60 kDa protein originally found in neutrophil azurophilic granules, on the neutrophil cell surface, and to a lesser extent, in

specific granules of eosinophils.[72,73] Subsequently, BPI was found to be widely expressed in various epithelial cells.[74] As its name infers, BPI selectively exerts multiple antimicrobial actions against Gram-negative bacteria, including cytotoxicity through damage to bacterial inner / outer membranes, neutralization of bacterial lipopolysaccharide (endotoxin), as well as serving as an opsonin for phagocytosis of gram-negative bacteria by neutrophils.[75–77] The high affinity of BPI for the lipid A region of LPS[78] targets its cytotoxic activity to Gram-negative bacteria. Binding of BPI to the Gram-negative bacterial outer membrane is followed by a time-dependent penetration of the molecule to the bacterial inner membrane where damage results in loss of membrane integrity, dissipation of electrochemical gradients, and bacterial death[79]. BPI binds the lipid A region of LPS with high affinity[80,81] and thereby prevents its interaction with other (pro-inflammatory) LPS-binding molecules, including LBP and CD14.[82] Since BPI binds the lipid A region common to all LPS, it is able to neutralize endotoxin from a broad array of Gram-negative pathogens.[75] The selective and potent action of BPI against Gram-negative bacteria and their LPS is fully manifest in biologic fluids, including plasma, serum, and whole blood.[83] In multiple animal models of Gram-negative sepsis and/or endotoxemia, administration of BPI congeners is associated with improved outcome.[84,85]

Implications and Future Directions for Clinical Practice

Postprandial endotoxemia is dependent on dietary selection. Ghanim, et al[16] found that a 900-kcal “American Heart Association” (AHA) meal of oatmeal, milk, orange juice, raisins, peanut butter, and English muffin prevented postprandial endotoxemia, whereas an isocaloric meal of egg and sausage muffin sandwiches with hashbrowns could not. The former meal also prevented rise in various markers of oxidative stress, NF-κB activity, TLR2 and TLR4expression. They later reported that addition of 300 kcal of orange juice to an endotoxemia-producing meal prevented any rise in circulating LPS.[14] Despite ingesting 1,200 kcal, the addition of orange juice also ameliorated indicators of inflammation and oxidative stress compared to a glucose drink and water only control. An assortment of foods and dietary components can reduce markers of inflammation including wheat bran,[86] olive oil,[87–89] walnuts,[87,90] and strawberry anthocyanin.[91] Additional studies are merited to determine wither the anti-inflammatory properties of these foods are related to an effect on LPS mediated inflammation. For example, parenteral administration of dietary components such as quercetin[92] and curcumin[93] can attenuate the effects of LPS infusion, although such a response from normal consumption of these food components remains to be demonstrated. An important point for those practicing clinical nutrition is that expression of ALPI decreases during fasting, and is restored upon refeeding.[94] This may underlie the benefit that patients receive from trophic feeding in acute illness.[63] More practical knowledge in this area is likely to emerge. For example, ALPI expression was augmented by an omega-3 fatty acid derived compound, Resolvin E1, setting a precedent that specific dietary components might influence expression of this protective enzyme.[69]

Much remains to be learned about the phenomenon of postprandial endotoxemia and how diet and gut microbiota mediate chronic inflammation. Despite results from animal experiments that convincingly demonstrate a role in pathology, whether postprandial endotoxemia mediates postprandial inflammation and pathology in humans remains to be

determined. It is tempting to speculate that interpersonal variability in LPS detoxification renders some individuals susceptible and others resistant to the outcomes of endotoxemia. To date, feeding trials have relied on healthy individuals who may have a higher capacity for LPS detoxification compared with morbid individuals. Nevertheless, the dramatic ability of specific foods and meals to prevent endotoxemia predicts that postprandial endotoxemia may become an important target for nutritional intervention.

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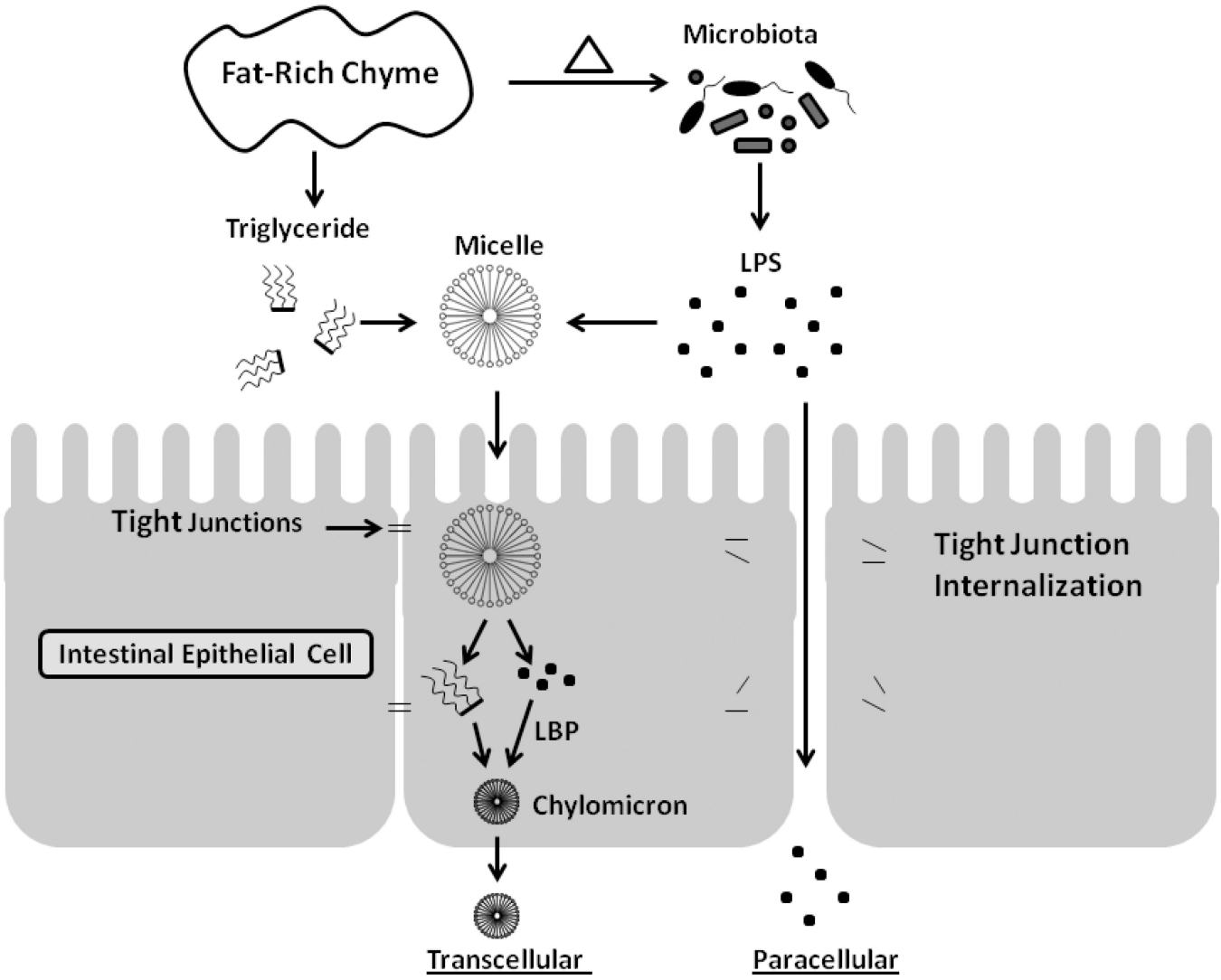

Figure 1.

Transcellular and paracellular transport represent non-exclusive pathways for LPS movement from the enteric lumen into circulation. In the transcellular model, lipid absorption serves as a vehicle for LPS, which is included in micelles and later incorporated into chylomicrons through interaction with LPS-binding protein (LBP). In the paracellular model, fat-rich chyme results in internalization of tight junction proteins by mechanisms that remain unclear. The impaired epithelial barrier then permits LPS to pass between epithelial cells.

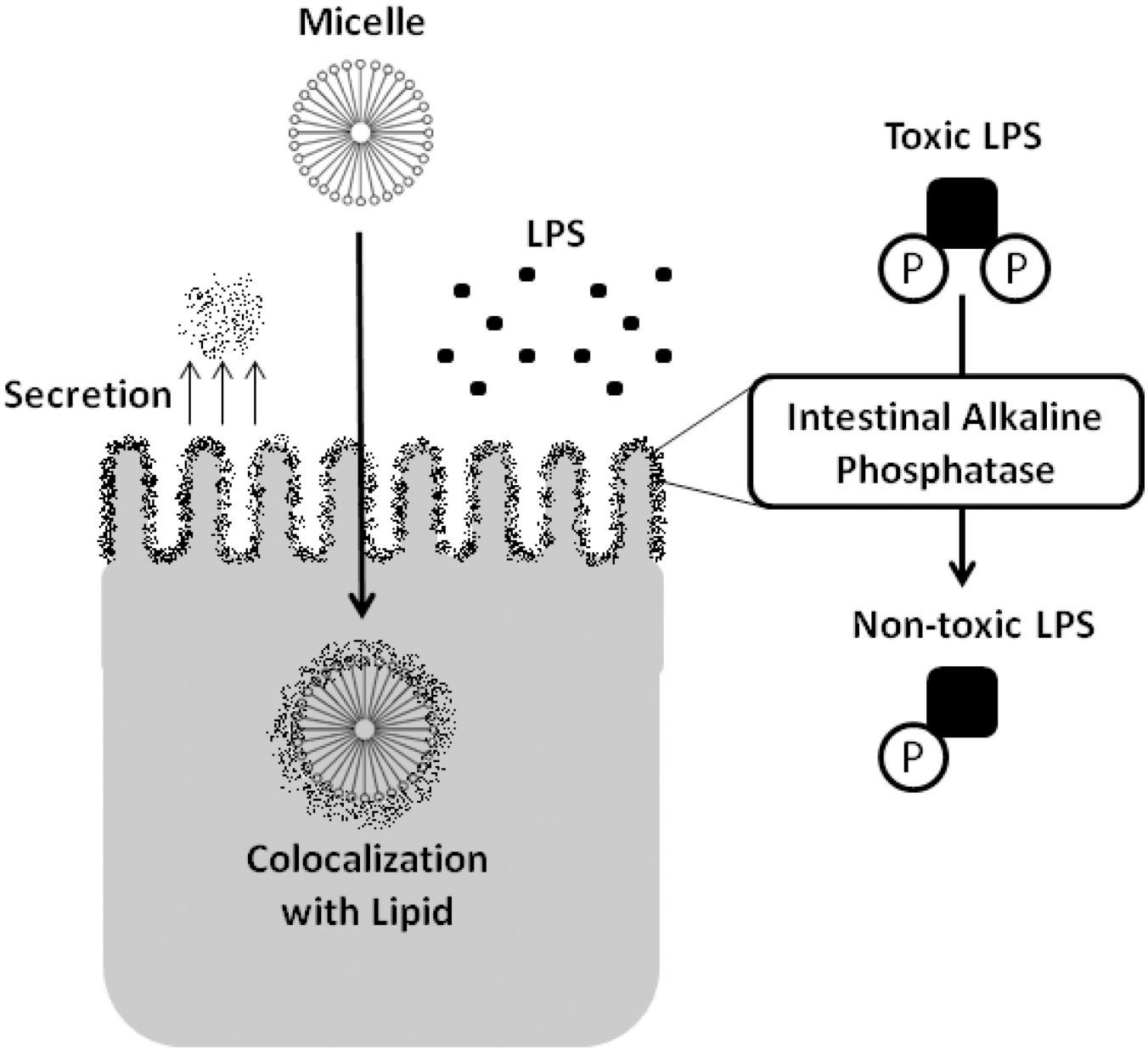

Figure 2.

Intestinal alkalkine phosphatase (ALPI) is an important enzyme in LPS detoxification. This highly expressed brush border enzyme is secreted into the lumen and co-localizes with intracellular lipid, maximizing contact with LPS. Under physiologic conditions, this enzyme converts the “toxic” LPS moiety (diphosphoryl lipid-A) to a less inflammatory form (monophosphoryl lipid-A). Of clinical importance, expression of ALPI decreases during fasting, but is maintained by enteral nutrition.

Table 1

Acute effects of a single high-fat meal on inflammatory indices in plasma/serum from healthy subjects

Test Meal	LPS	IL-6	TNF-α	CRP	Reference
910 kcal (50% fat, 15% protein, 39% CHO)	↑		↔	↔	Ghanim[16]
882 kcal (33% fat, protein/CHO not reported)	↑	↑			Laugerette[13]
900 kcal (50% fat, protein/CHO not reported)	↑			↔	Erridge[17]
923–970 kcal (42–45% fat, 6–12% protein, 40–46% CHO)		↓	↓	↓	Nestel[95]
778 kcal (60% fat, 12% protein, 28% CHO)					Esposito[96]
1800–2200 kcal (64% fat, 18% protein, 18% fat)		↑	↓	↔	Blackburn[97]
1076 kcal (67% fat, 4% protein, 30% CHO)		↑	↔		Orban[98]
760 kcal (59% fat, 12% protein, 29% CHO)		↑	↑		Nappo[99]
Kcal not reported: 50 g fat and 3.75 g glucose/m^2 body surface area (97% fat, 3% CHO)		↑		↔	van Wijk[100]
658–869 kcal (68–77% fat, 9–12% protein, 16–22% CHO)		↓	↔		Manning[86]
485–543 kcal (50 E% fat, 20 E% protein, 30 E% CHO)		↑			El-Khoury[101]
910 kcal (50% fat, 14% protein, 36% CHO)				↑*	Aljada[102]
415 kcal (100% fat)			↔ or ↓		Papageorgiou[103]
621 kcal (76% fat, 3% protein, 21% CHO)		↓		↔	Tholstrup[104]
748 kcal (71% fat, 5% protein, 23% CHO)		↑	↓	↔	Poppitt[105]
553 (51% fat, 11% protein, 38% CHO)				↔	Igarashi[106]
879 kcal (51% fat, protein/CHO not reported)				↔	Tsai[107]
675 kcal (100% fat)				↔	Zahedi[108]
1000 kcal (60% fat, 13% protein, 27% CHO)		↑			Lundman[109]
Kcal not reported. 1 g fat/kg (100% fat)		↑		↔	Dekker[110]
1600–2200 kcal (64% fat, 18% protein, 18% CHO)		↑	↔ or ↓	↔	Payette[111]

Table 2

Acute Effects of LPS infusion on inflammatory indices in plasma/serum from healthy subjects

LPS Dose	IL-6	TNF-α	CRP	Reference
2 ng/kg	↑	↑	↑	van der Meer[112]
2 ng/kg	↑	↑	↑	Dorresteijn[113]
2 ng/kg	↑	↑		Sauermann[114]
2 ng/kg	↑	↑		van Eijk[115]
2 ng/kg	↑	↑		Soop[116]
2 ng/kg	↑	↑		Mayr[117]
20 IU/kg			↑	Steiner[118]
20 IU/kg	↑	↑	↑	van Zee[119]
4 ng/kg	↑	↑		Pajkrt[120]
4 ng/kg	↑	↑		Pajkrt[121]
4 ng/kg		↑		Dekkers[122]
4 ng/kg	↑	↑		de Jonge[123]
4 ng/kg				Lauw[124]
4 ng/kg	↑	↑	↑	Bunnell[125]
0.8 ng/kg	↑	↑		Reichenberg[126]
4 ng/kg	↑	↑	↑	Branger[127]
4 ng/kg	↑	↑	↑	Lynn[128]
4 ng/kg	↑	↑		van Bockel[129]
4 ng/kg	↑	↑		de Kruif[130]