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Fat and the gut: More than empty calories

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Traditionally, studies investigating the pathogenesis of gut injury have focused on the splanchnic circulation and systemic host factors, because it is well recognized that shock as well as other major insults such as burns, trauma, and pancreatitis lead to shunting of blood away from the gut, resulting in an intestinal ischemia–reperfusion injury as well as an ischemia–reperfusion-induced gut inflammatory response. Although systemic factors are undoubtedly important, the basic notion behind this study by de Haan et al (1) showing that a high-lipid diet can protect against hemorrhagic shock-induced gut injury is that factors operating from the luminal side of the gut can modulate gut injury induced by systemic insults. This concept that luminal factors and the luminal response to splanchnic ischemia are important in modulating gut injury is being increasingly recognized. In fact, the hypothesis that the luminal contents of the gut, including the mucus gel layer, pancreatic proteases, and the gut flora as well as the response to specific nutrients, are critically involved in the pathogenesis of ischemia–reperfusion-induced gut injury and the subsequent development of gut-induced multiorgan deficiency syndrome has been recently reviewed (2). One example supporting this concept of luminal modulation of systemic insults comes from studies from our as well as the laboratory of Schmidt-Schonbein documenting that luminal pancreatic proteases are necessary for the development of gut injury and subsequent gut origin sepsis and multiorgan deficiency syndrome after hemorrhagic shock (3,4). A second example comes from a study of systemically administered endotoxin (5), in which it was shown that endotoxin-induced gut injury was the result of the local action of bile-derived tumor necrosis factor acting on the luminal side of the gut mucosa rather than the systemic hemodynamic consequences of endotoxin. Additionally, it was recently shown that the enteral administration of high-molecular-weight polyethylene glycol (a mucus surrogate) prevented lethal gut origin sepsis (6). In fact, based on the gut hypothesis of multiorgan deficiency syndrome, a number of enteral nutritional formulas have been developed whose goals are to limit gut injury and increased gut permeability by providing gut-specific as well as total body nutritional and physiological support. The biology behind these diets was that supplying enterocyte-specific nutrients as well as immunomodulating factors in the enteral diet would be clinically beneficial by limiting gut injury as well as the gut and systemic immunoinflammatory responses. Because the development of successful clinical therapies is based on complete knowledge of the mechanisms of the injuries they are being developed to treat, the current study by de Haan et al (1) has expanded our knowledge by indicating that activation of the CCK receptor by a high-lipid enteral diet can limit gut injury through activation of the vagus nerve thereby inducing the cholinergic anti-inflammatory response. That said, let us look at the biology of the response suggested by this work.

Based on the use of antagonists for both cholecystokinin receptors CCK1 and CCK2, the authors concluded that the protective effects of the high-lipid enteral diet was mediated through activation of CCK receptors in the gut. Assuming the specificity of these antagonists, the differential distribution of these receptors may suggest a predominant contribution of the CCK1 receptor in this protective response. Unlike CCK2, which is mainly expressed in the central nervous system and related to anxiety and the perception of pain, CCK1 is mainly expressed in the intestine and induces enzyme secretion by the pancreas, gastric acid in the stomach, and intestinal motility and satiety. The authors

previously reported that a high-fat diet inhibits serum tumor necrosis factor, interleukin-6, and increased intestinal permeability and endotoxemia during hemorrhagic shock (7). These effects appear to be mediated by the vagus nerve because they were prevented by surgical vagotomy (7). Similar results were reported in endotoxemia indicating that electrical vagus nerve stimulation attenuates systemic tumor necrosis factor by inhibiting its production in the spleen through the alpha7 nicotinic acetylcholine receptor (8–10). Consistent with this notion was that vagal inhibition of the inflammatory response and vagus nerve stimulation failed to attenuate tumor necrosis factor production in the alpha7 nicotinic acetylcholine receptor R knockout mice or splenectomized animals, and acetylcholine, the principal neurotransmitter of the vagus nerve, failed to inhibit endotoxin-induced tumor necrosis factor production in alpha7 nicotinic acetylcholine receptor-deficient splenocytes (9,10). Together, these results suggest that one aspect of vagus nerve protection of the intestine may be by inhibiting splenic and or hepatic tumor necrosis factor production and preventing its delivery into the intestine through the bile duct. In agreement with this hypothesis, bile-derived tumor necrosis factor has been shown to mediate intestinal pathology in endotoxemic shock (5). Although future studies are required to evaluate this mechanism in hemorrhagic shock, recent studies do indicate that alpha7 nicotinic acetylcholine receptor agonists attenuate inflammatory cytokine production and prevent organ damage in hemorrhage (11). In addition to inflammatory cytokines, cholecystokinin and the vagus nerve also modulate other factors affecting intestinal integrity, including pancreatic and intestinal digestive enzymes and proteases, which will need to be evaluated.

Although intriguing, this study does have some limitations. First of all, the model is a purely gut ischemia shock model, because the rats are not volume-resuscitated. Because in clinical circumstances, bleeding patients will receive volume to restore their blood pressure and reperfusion does contribute to gut injury, the effects of reperfusion will need to be considered. Secondly, the 60- and 90-min time periods studied is relatively short. Thus, whether the protective responses observed with the high-lipid enteral feeding persist for hours and hopefully days will also need to be considered before any final conclusions can be reached. Haan et al (1) also suggest that the vagus nerve may protect the intestine by inhibiting mast cell proteases. Although CCKR antagonists increased the serum levels of rat mast cell protease in the animals with a high-fat diet, the specificity of this mechanism remains controversial. Indeed, both the low-fat and high-fat diets decreased serum rat mast cell protease in a similar proportion 30 mins after hemorrhage. Thus, as already mentioned, these results warrant time course experiments to determine whether these effects are similar over time or whether CCKR antagonists can also increase serum rat mast cell protease in low-fat diet-fed or fasted animals. Likewise, future studies with vagotomized animals and cholinergic antagonists would also be required to confirm whether this effect is mediated by the vagus nerve and cholinergic receptors in the mast cells. Additionally, because hemorrhage increases intestinal bacterial leakage and mast cells protect against bacterial infection and sepsis, general pharmacologic inhibition of mast cells may not generate an overall beneficial effect.

In summary, although the exact mechanisms by which the gut becomes injured and contributes to systemic inflammation and organ injury during shock and stress remains to be fully defined, we are getting closer.

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