Saturated Fatty Acids and Inflammation: Who Pays the Toll?

Alan Chait, Francis Kim

Since the discovery that obesity is associated with macrophage accumulation in adipose tissue, mechanisms by which adipose tissue becomes inflamed, resulting in insulin resistance, have remained elusive. Several studies have demonstrated that saturated fatty acids (SFAs) stimulate adipose tissue inflammation by a process that involves Toll-like receptor 4 (TLR4), a receptor that binds bacterial lipopolysaccharide (LPS). TLR4 is a pattern recognition receptor that plays a key role in the innate immune response. The observation that TLR4 deficiency protected against insulin resistance suggested that TLR4 was the link between diet excess and insulin resistance. Attenuation of diet-induced insulin resistance in TLR4-mutant macrophages demonstrated that saturated fatty acids (SFAs) stimulate adipose tissue inflammation. TLR4 activation by SFAs involves effects of SFAs on TLR4 receptor number, dimerization, lipid rafts, and the balance between saturated and unsaturated fats. Although LPS binds TLR4 by a process that also involves CD14, radiolabeled SFAs did not bind directly to TLR4. Although one study showed that free fatty acids failed to enhance TLR4 dimerization, another showed that SFAs induce TLR4 dimerization and recruitment into lipid rafts, a potentially important mechanism by which TLR signaling is modulated by dietary fats. For example, altering lipid composition in rafts by incorporating docosahexaenoic acid resulted in disruption of TLR4 recruitment into lipid rafts and reduced downstream signaling. However, SFAs do not activate downstream targets of TLR4 directly. One study showed that stimulation of TLRs by fatty acids was due to minor LPS contamination of the albumin to which they were complexed, although other studies have taken considerable care to remove LPS. TLR4 expression is increased in patients with atherosclerosis, and the expression of TLR4 can also be enhanced by high blood glucose and oxidized low-density lipoproteins. Thus, upregulation of TLR4 expression may enhance the sensitivity of cells to inflammatory signaling. The propensity for the activation of TLR signaling may also be affected by the balance between stimulatory SFAs and inhibitory n-3 fatty acids. This might be important because immune cells exposed to plasma SFAs would be continuously activated if not for the inhibitory fatty acids.

The study by Schwartz et al in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* sheds new light on how SFAs cause adipose tissue inflammation. In this study THP-1 monocytes and human monocytes and macrophages exposed to SFAs demonstrated enhanced interleukin-8 and interleukin-6 expression in response to low dose LPS. Amplification of the LPS response required metabolism of the SFAs to ceramide, and it involved activation of C-\(\gamma\) mitogen-activated protein kinase. It demonstrates a novel way by which fatty acids might modulate the innate immune response, i.e., by their metabolites cooperatively enhancing TLR/nuclear factor \(\kappa\)B–mediated inflammation. LPS frequently circulates at low concentrations in the bloodstream because of absorption from the bacterial flora of the gut, subclinical infections, or food contamination. The simultaneous ingestion of foods rich in SFAs might amplify stimulation of inflammatory gene expression in macrophages. Minimal contamination of reagents with LPS might also explain some of the in vitro findings with SFAs. However, they do not explain why some fatty acids have no effect whereas others inhibit inflammatory gene expression, because they all are complexed with albumin, the most likely source of LPS contamination.
Deficiency of TLR4, confined to macrophages, was not associated with a reduction of macrophage accumulation in adipose tissue or insulin resistance in response to a SFA-rich diet in mice. However, total body TLR4 deficiency or a nonfunctional mutation of the TLR4 gene was associated with reduced insulin resistance and macrophage accumulation in response to a high-fat diet. If the findings with deficiency of TLR4 in macrophages are confirmed, this suggests that TLR4 on adipocytes rather than macrophages might play an important role in macrophage accrual and insulin resistance in response to a diet rich in SFAs. One way that this might work is by adipocytes generating monocyte chemotactic factors, which play an important role in macrophage accumulation and insulin resistance in adipose tissue. Activation of TLR4 by SFAs on endothelial cells also may lead to insulin resistance at sites such as the artery wall, perhaps suggesting a common mechanism for fatty acid–induced insulin resistance in several cells, such as adipocytes, B cells, and myocytes. The current study thus adds a new level of complexity to an evolving story concerning the role of dietary SFAs in the pathogenesis of insulin resistance. Future studies concerning the interplay of fatty acids, LPS, and TLRs are likely to further unravel the intricate web that leads to adipose tissue inflammation.

Disclosures

None.

References

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